MARCH 1951

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

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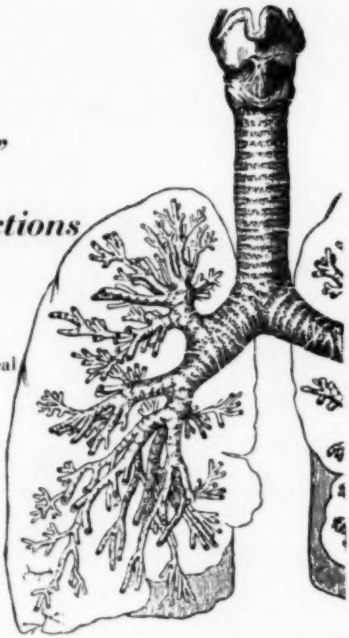

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2. *Herrell, W. E.; Heilman, F. R.; Wellman, W. E., and Bartholomew, L. A.: Proc. Staff Meet. Mayo Clin. 25:183 (Apr. 12) 1950.*
3. *Knight, V.: New York State M. J. 50:2173 (Sept. 15) 1950.*
4. *Dowling, H. F.; Lepper, M. H.; Caldwell, E. R., and Spies, H. W.: Ann. New York Acad. Sc. 53:433 (Sept. 15) 1950.*
5. *Schenck, H. P.: M. Clin. North America 34:1621 (Nov.) 1950.*

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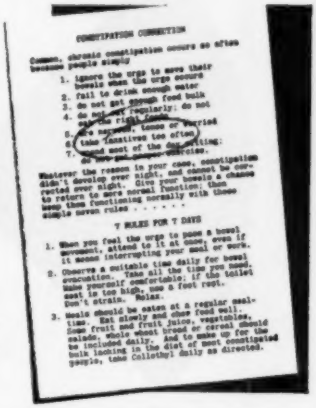

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1. Rev. Gastroenterol. 14:558, 1947.
2. J. Oklahoma M. A. 43:360, 1950.
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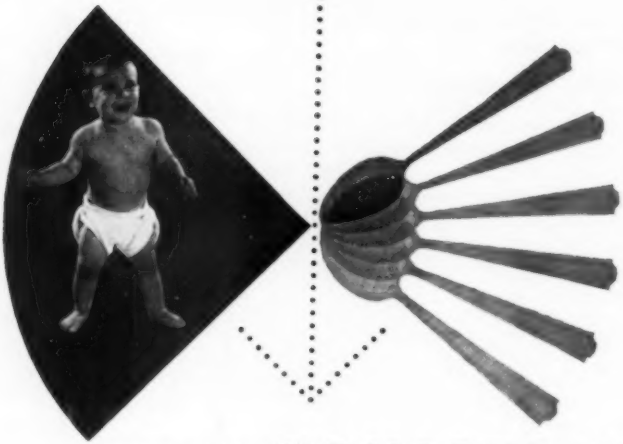

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MAHLON ASHFORD, *Editor*

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BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 27, NO. 3 MARCH 1951

INAUGURAL ADDRESS*

WILLIAM BARCLAY PARSONS

President, The New York Academy of Medicine

ONE feels quite naturally somewhat overwhelmed by being in the position I find myself in tonight, considering the list of distinguished men who have preceded me and in particular my immediate predecessor Dr. Watson who has labored so untiringly in the interests of the Academy and has brought such wisdom and inspiration to all its activities. Any previous experience in addressing medical meetings on some subject closely identified with one's professional activity, therefore with reasonable confidence and perhaps some authority, on this occasion in the immediate problem facing me, is nearly worthless. One of the really difficult things to do is to say thank you with sincerity and due humility. Both of these sentiments run strongly in me at this moment, but I really cannot express my very real and deep appreciation of the honor you have paid me in selecting me to preside over the activities of The New York Academy of Medicine for the coming two years. To each of you as to me the Academy has meant much in the past. We all know of its service to the medical profession and to the public at large. Knowing of the wisdom, unselfishness and zeal of its Director and of the various committees and their Chairmen, we can anticipate further growth in

* At the Annual Meeting of The New York Academy of Medicine, January 4, 1951.

usefulness to the profession and the community, and only because of them can have full confidence in its immediate future. It is a great honor to be its President, and I would be less than human if the pleasure and gratification I feel were not indeed nearly immeasurable.

In casting about for a subject to discuss with you tonight the choice seemed to lie between the future in terms of the present and the present in terms of the past. While thinking about the former, namely the future, some remarks of Walter Lippmann in an unpublished address made last spring came to mind. He pointed out that members of our generation, and he was speaking of his and mine which also applies to many here this evening, were born, were educated, and began their life work in an era of established and apparently permanent peace. This state of peace with its implications as to the future of each individual was taken for granted. There was such a feeling of security in the present and future of that date that a young man starting his life work could look forward with confidence to a good living for himself and his family provided that he was reasonably intelligent and exhibited more than average diligence. Further he knew that he could, by practicing moderate economy, lay aside sufficient funds to provide for his own old age as well as help for his children. As Lippmann expressed it a flood came in August 1914 that is still engulfing us. Unlike the biblical flood of water this was a flood of battle, blood, suffering, dissension and uncertainty. After a financial crash and depression, and a second world war, the world is still faced with grievous difficulties. Please do not blame me for hesitating to indulge in any prophetic consideration of the future, particularly in view of the situation of the armed forces of the United Nations in Korea, the fact that the younger members of our profession are being called to active duty, and the further fact that this city and state, as well as others, are seriously engaged in preparing to cope with the catastrophic results of an atomic bomb explosion. To attempt to predict how and when this Academy may have to deal with what would seem fruitless. It is certain, however, that its fellowship will not be found wanting in any future period of trial, any more than they have been in the past. Nevertheless, it is most clear that it is incumbent on each of us individually and on all of us collectively to keep thinking soberly and constructively on these problems of the day, unpleasant and discouraging as they may be. It may seem that they are far from our professional lives but I venture to suggest that they may not be so, certainly not

in some of their political aspects. Only if we are clear in our individual and collective thinking will we be able to protect the professional principles and way of life that we not merely hold dear but are convinced are important to the health of the country and the future of medicine.

After indulging in these sombre thoughts as to the future a ray of light appeared in considering the past. The thought emerged that it might be of interest to draw attention to the advances that have been achieved in medicine in general as exemplified in the metamorphosis of the surgeon since my undergraduate days, and perhaps to draw some conclusions therefrom. During these years there has emerged a very different type of person from the superior sort of technician that the surgeon of a generation ago was held to be by the majority of physicians of that day; and perhaps rightly so. Of course in all branches of medicine the change has been dramatic. As examples from the laboratory and the medical wards of this day, pH, not the hospital but the physicochemical entity, had not even been thought of, and typhoid fever was still an important problem in all the hospitals in the city each summer.

As many of you know, I have had some interest in surgery of the thyroid for thirty years. In the pre-iodine era nearly every patient operated on for Graves' disease exhibited postoperative thyroid storm and even in the better clinics the mortality was considerable. With the introduction of iodine in 1923 an immediate drop in mortality occurred and this improvement has continued so strikingly in recent years, partly with the advent of other drugs, that the mortality is merely a fraction of one per cent in large centers. Other factors were also involved in this satisfactory process, such as a better psychological approach, technical operative training of the surgeon and, what was of great importance, the introduction of a program of nutrition greater than the theoretical needs of the individual with emphasis on an abundance of protein. Twenty-five years ago the late Walter Palmer with Sloan and Carson studied the protein metabolism in hyperthyroidism and showed that these people were in negative protein balance which could be corrected by a sufficiently high protein intake. It is not subject to proof that this stimulated the recognition by surgeons of the importance of nutrition in general and protein metabolism in particular in the pre- and postoperative care of surgical cases, but certainly it was at about this time that there appeared an understanding of this fact which rather rapidly in a few years began to be applied elsewhere, in such major high risk problems of that

day as gastric, intestinal and other operations now taken as matters of course, as well as in cases with prolonged sepsis or other debilitating processes in which poor nutrition was, among other factors, perhaps more important in relation to recovery than the underlying disease. Before long greater familiarity with hepatic and renal pathological physiology indicated the role therein of sugar and protein metabolism and electrolyte exchange.

Coincident with an increasing interest in nutrition and in liver and kidney physiology, studies on the mechanism of shock began to throw light on functions of the circulating blood and its constituents, hitherto unknown. Transfusion of blood and the infusion of salt solution, glucose and even gum acacia, of brief popularity, by the time of World War I had been in use but on really only an empirical basis. Far too often even up to recent years various fluids and in particular sodium chloride were given in too large amounts. Before this Academy in December 1948 the late John Lockwood with Randall, in discussing electrolyte studies in surgical patients, gave due credit to those who had labored in the basic science laboratories and to the discoveries by physicians in various fields. He was glad to grant that men like Folin, Gamble, Peters, Van Slyke, Darrow and their co-workers, as well as many others, did the true basic work. He pointed out, however, that the surgeon is called upon to meet rapid, often even emergency intercompartmental fluid and electrolyte shifts, which sometimes are the result of the type and amount of fluid he has administered. Surgeons began to recognize that they must be prepared to handle these problems themselves. From the work of surgeons like Coller and Maddock, Elman, Moore, Evans and many others has come a better understanding of the rapid shifts in fluid and electrolyte balance that follow trauma, anesthesia, burns, vomiting and intestinal drainage by tube or fistula. A similar state of affairs is present in regard to the use of whole blood or its derivatives. The estimation of blood volume, with its components, is a commonplace in most surgical services in cases of dehydration, surgical jaundice or blood loss from whatever cause. The simple red blood cell count and hematocrit determination under many circumstances do not indicate the red cell mass deficiency. In obstructive jaundice, for example, there is commonly an increase in plasma volume which necessitates the greatest care in fluid and sodium administration, and indicates the dangers from over-transfusion. If, as Lockwood expressed it, the surgeon desires a place in the company of

scientific medicine he must understand these principles, be able to secure the data that will indicate deficiencies, and be prepared to remedy such deficiencies before an irreversible situation has been established.

These are a few examples of the biochemical and basic physiological phenomena commonly handled nowadays in the surgical wards and laboratories. It would be pointless to inflict on you a list of the various operative manoeuvres now being done; they are of course of great magnitude and familiar to all of you. One striking example of the kind of organic problem being attacked these days is that of heart and great vessel surgery. Up to just a few years ago these structures had enjoyed a sort of privileged privacy. That is now a thing of the past and no viscus now remains that is immune to surgical trespass. In fact the time is almost at hand when extra-corporeal circulation may be maintained to allow for even more extensive manoeuvres designed to correct circulatory disabilities.

These few points should suffice to indicate the scope and character of modern surgical therapy in all its branches. This greatly widened scope has resulted only slightly from purely technical developments in the actual performance of any operation, because any well-trained surgeon should rapidly develop new technical facility. The superb record in the treatment of casualties in all theatres in World War II was achieved because there were available a host of well-trained surgeons who were not merely expert operators but who also in their training had been exposed to laboratory methods and who were familiar with the psysiological and circulatory disturbances that follow the receipt of severe trauma and how to avoid or correct them. All surgeons are not expert laboratory workers by any means, but in all University hospitals throughout the country one can find surgical laboratories busy with a host of studies of the greatest variety in which the surgical residents at some time in their training have taken part. Some of these studies are along new lines; but it is one of the eminently fine characteristics of the modern surgeon that in most of these research activities he is using information produced by medical and basic science laboratories that is applicable in situations peculiar to surgery, either through the particular disease itself or the disturbances consequent to the operation.

The point I am trying to make, and perhaps have belabored unnecessarily because of my interest in it, is that the surgeon has progressed far from the position of being merely a technician. It is true that part of

his training fits him for the performance of the therapeutic incident of the operation; but the rest of his training, by making him concerned with far more than that, has placed him alongside the internist in the practice of modern scientific medicine. We have progressed by leaps and bounds in this generation of ours in all branches of medicine, but still have far to go. Animal experimentation, free and independent research along a wide variety of related and often seemingly unrelated lines, rivalry but yet coöperation between institutions, and the greater awareness by scholars in the basic science laboratories and in the clinic of a mutual inter-relationship have been some of the contributing factors in this development shared by all branches of medicine. In all of this progress our Academy has played its part in its Stated and Section meetings, in its great Graduate Fortnight, through its lectures and publications and through the devoted labors of its various committees.

The President of the United States has declared the existence of a State of Emergency. No one knows what the coming months and years will bring to all of us. If and when general mobilization comes, each of us will have his part to play. Personally I believe that theoretically general mobilization is the fairest and best method of utilizing the manpower of the country effectively in the particular situation facing us, although the problem of personnel assignment would be prodigious and the risk of permanence considerable. The danger implicit in starting this type of governmental regulation of the lives of all citizens is clear, although by no means the certainty that would be the case were we defeated by Russia. Moreover, one cannot help wondering whether such a move on our part as general mobilization would not be pleasing to communists as being the first step along the road to an all-powerful central government. If another post war period comes with widespread material destruction, dislocation of the lives of the people, hunger, sickness and want, the temptation and perhaps the need to continue strong central control might be irresistible. It requires but little imagination to foresee how all things medical would fare under such circumstances. One of the duties, perhaps the only important duty of this Academy, if such a time ever comes, and God grant that it will not come, may be to exert its influence to maintain the freedom of medical education, research and practice so that the gains won by this generation may be consolidated and become the basis for even greater progress in the next and ensuing generations.

In the meantime we physicians, as physicians, do have an opportunity. Two forms of contagion are beginning to spread that we can recognize and help to check. One is a sort of mental blindness that fails to see what is going on in the world and thinks that we can fold up in our shell like an armadillo and be safe; but the shell of an armadillo is not strong enough to withstand more than limited pressure, nor can we be safe unless we are strong, and this will not be achieved by thinkless wishing, as someone has called it. The other contagion is selfishness, sired by sloth out of greed, which desires business as usual and let the other fellow do it. Illness of body and mind, pain and death have always been the constant adversaries of physicians, and we know them well, respecting but not fearing them. We know the need of adequate preparation and prompt decision in coping with disease, but also we know what these two can accomplish in mitigation if a threatened condition becomes established. Does not this apply in the case of the serious epidemic now threatening the world? It should be clear to all that for quarantine purposes we must help the other free peoples of the world and buckle to the business of making ourselves strong regardless of the rigorous disciplines required, or the epidemic will spread inevitably. A crowd is made up of individual persons and so is a nation. There is a little time, and it is not for us physicians perhaps to sound a clarion call as Churchill did in the dark days of the Battle of Britain; but we can and must make our influence felt on the individuals with whom we come in contact as friends and acquaintances, or in the extraordinary relationship of doctor to the patient and his family, so that we may help the selfish to understand that their own interests are at stake, and make the blind see the true picture now unfolding.

ADDRESS OF THE RETIRING PRESIDENT*

BENJAMIN P. WATSON

ON December 31, 1950 my two years of office as your President came to an end. This has brought with it a sense of relief and at the same time one of regret, the latter far outweighing the former for, whilst your president must give much of his time and effort to his duties, there is more than ample compensation in the interest of the work and in the mental stimulus which comes of participating in the many activities which go on within these walls.

There are also outside interests for, occupying as it does an honored place in the community, The New York Academy of Medicine through its President and other officers is frequently called upon to participate in public functions and ceremonies. For me, the most notable and at the same time most terrifying of these was when I gave an address in the Cathedral of St. John the Divine at a full church service, commemorating the centenary of St. Luke's Hospital. That will always remain for me a vivid memory for it was the first time that I had, as the Scots put it, "wagged my heid in a pu'pit."

Other addresses which I have been called upon to give have come more within the range of my experience augmented as that has been by the briefing which I invariably asked for and never failed to receive from the Director and other officers of the Academy.

Whilst it is customary for the President to give a short account of the work done at the end of each of his two years of office it must be realized that our activities are not demarcated on a calendar basis but are a continuing performance. The permanency in office of the Director and Executive Secretaries, and the limited changes in the chairmanship and personnel of our standing committees make it possible to carry on all our accepted functions from year to year. To do that and at the same time prevent these from becoming mere repetitive routine requires constant watchfulness and a great deal of hard work on their part. And always there are new problems coming up calling for investigation; new challenges to be met; new methods to be explored and exploited. It is to some of the more recent of these that I shall call your attention.

* Given 4 January, 1951, at the Annual Meeting of The New York Academy of Medicine.

A few years ago the Committee on Medical Information, through its director, Dr. Iago Galdston made arrangements whereby the Lectures to the Laity were broadcast to the general public over radio station WNYC. Stimulated by the evident success of this venture they began, eighteen months ago, to explore the possibilities of making tape recordings of some of the scientific papers and round table discussions held here, having them transferred to discs and from these making FM broadcasts over a local station. Furthermore, it was envisaged that these discs might be made available to FM stations in other localities and to medical organizations and individuals all over the world for gramaphone reproduction. Here was a new method for the transmission of medical knowledge.

A small subcommittee from the Committees on Medical Information and Medical Education was appointed with Dr. Norton Brown as Chairman. Thanks largely to his unremitting energy and that of Dr. Galdston the dream has been transformed into reality. The first FM broadcast "for doctors only" was made in January 1950. Since then there have been broadcasts of three series of eight lectures each, all of them originally delivered here. The broadcasts are made over WNYC-FM on a specified day each week and at a fixed time previously announced. They naturally reach a much larger audience than could ever assemble here, for already many doctors in and beyond the Metropolitan area are reserving this time, happy in the thought that they can have a quiet evening at home and also be acquiring knowledge of things new in medicine. Many laudatory letters from doctors have been received and requests for the discs have come from medical organizations from all over the world as well as from the State Department which has requested transcriptions for the Voice of America and for the Embassies and Consulates in countries carrying English programmes.

The Academy of Medicine may well be proud of this pioneering effort in medical education. It has been made possible only by the donation of time and service by radio station WNYC and by the wholehearted support of its director, Mr. Seymour N. Siegel. We tender them our grateful thanks. Even with this generous contribution it is estimated that the additional cost to the Academy will be in the neighborhood of twenty-six thousand dollars a year. This addition to our budget will have to be met by new endowments, grants and donations. The committee has already enlisted some financial support but we must

look to the Fellows to help out by interesting public spirited individuals in the project.

As all of you know, there are few radio broadcasts of educational value, for these have little appeal to commercial sponsors of radio programmes. The New York Academy of Medicine therefore thought it right to join with other scientific, educational and cultural organizations in petitioning the Federal Communications Commission for reservation of at least 20 per cent of television channels for educational purposes. Unless such reservation is made now the vast possibilities of television as an educational medium may well be lost for the future. That it has such possibilities was demonstrated at our 1950 Twenty-Third Graduate Fortnight on the "Musculo-Skeletal System" at which in addition to the usual evening lectures, morning panels, hospital clinics and scientific exhibits, there were arranged six televised telecolor programmes of surgical operations. These were acclaimed as of great teaching value.

The Committee on Medical Education, ever-watchful for what is new and important, arranged a special conference and round table discussion on cortisone and ACTH in which there took part many of the pioneers in the discovery and clinical application of these new and spectacular therapeutic agents. It was from a part of this conference that our first FM radio broadcast was made.

Under the auspices of the Committees on Medical Information and Medical Education an informal conference with the Deans of the five medical schools in the Metropolitan area was held to discuss ways and means of making the Academy with all its facilities better known and more useful to their students. As a result a plan is being worked out whereby all of the freshmen in these five schools will, each year, be extended an invitation to visit the Library, meet the Officers and Fellows and have explained to them the ways in which we can be helpful. They will come in small groups each made up of students from all five of the schools so that they may fraternize and learn from each other what goes on in schools other than their own. There is also under consideration the possibility of conducting for these students a short course in the history of medicine planned along lines with more interest and appeal than those generally given. Our great collection of historical lore in the library and our ability to secure the proper speakers would seem to make this eminently practical.

Last year in my annual report I told of the symposium which was

held in conjunction with the New York County Lawyers Association on the subject of "Law, Medicine and the Unstable Family." Always on the outlook for new contacts for the interchange of ideas, the Committee on Medical Information recently organized a conference with ministers of religion to explore the possibilities of greater coöperation between the clergy and the medical profession in treating the sick, especially the sick in mind. Thirty members of the clergy of all faiths and denominations and twenty-seven interested physicians, together with committee members took part. The transactions of this conference are in the course of preparation for publication. They should supply a basis on which to build new methods of approach to many forms of human distress.

That the public is interested in and concerned about problems of the mind and their impact upon human welfare is shown by the overflowing attendance at the Laity Lectures whenever these treat of a psychological or related subject. We are all coming to realize more and more how important is the psychological approach. The subject deliberated at our last Eastern States Health Conference was the Psychological Dynamics of Health Education. The committee on Public Health Relations is at present exploring means of lessening the incidence of mental illness by community action. Today we are preparing ourselves for the possibility of major disaster from atomic attack. In densely populated areas such as New York it is conceivable that should such attack come, there would be more casualties from panic than from the direct action of the bomb. The Committee on Medical Information has therefore begun to plan a conference of those with expert knowledge to consider the subject of panic and to formulate methods of minimising it by mass enlightenment and conditioning of the public. In this it is hoped to enlist the coöperation of our municipal departments, health and educational agencies and Civil Defense Authorities.

In the broad domain of Public Health the Committee on Public Health Relations has given detailed consideration to a number of subjects, many of them referred to it by our various health agencies. The Study of Neonatal Mortality is well into its second phase which is concerned with the causes of neonatal deaths and the possibilities of their prevention. A subcommittee of nine obstetricians, nine pediatricians and three pathologists acting with Dr. Chandler Foot as Director and five field workers makes a detailed study of each death reported. It is ex-

pected that the study will be completed by May of this year and that the report will be ready shortly thereafter.

A prolonged study of the relationships between funeral directors and hospitals concerning autopsies resulted in the preparation of a "Manual of Procedures upon the Occurrence of a Death in Hospitals of the Metropolitan Area," and also a wall chart indicating acceptable autopsy room procedure. These two documents were published under a subvention from the United Hospital Fund and distributed to all hospitals in the Greater New York area. The usefulness of this work is attested by the fact that after receiving the initial copies, hospitals requested large numbers of these pamphlets. The first edition of 5,000 copies has been almost exhausted, and again with a grant from the United Hospital Fund, a second printing was ordered. Out of the work of this group has come also the formation of a joint committee representing the Academy, the Greater New York Hospital Association, the New York Pathological Society, and the Metropolitan Funeral Directors' Association to follow up the recommendations in the Manual.

The Commissioner of Hospitals requested the Committee's advice as to ways in which the city's provision of convalescent care for its charges could be made more effective. The Committee's report suggested that the Department of Hospitals consider incorporating convalescent units in any new hospitals that may be built, and that in the meantime, ample use be made of existing institutions, and that home care be tried whenever possible. Changes in the Department's procedure to facilitate admission of patients to convalescent institutions, to simplify the financial arrangements, and to broaden the basis for approval of convalescent care were recommended.

Other matters which the Committee has studied and on some of which it has issued reports were the Care of Mental Patients in Proprietary Hospitals, Electro-shock therapy, Air pollution and Smoke control, Practical nurses for Home Service, Street Cleaning, Fluoridation of City Water. These will be published in the annual report.

A great deal of the time of the Committee was devoted to various legislative proposals with public health implications. Among other things, it dealt with the establishment of a state mental health council comparable to the Advisory Health Council of the State Department of Health, which was approved; it opposed the amending of the Medical Practice Act by additions proposed on behalf of radiologists; it endorsed the

bill for licensing of physiotherapists and one for the lowering of the age of licensure for practical nurses from 19 to 18, it was in favor of a provision for indeterminate prison sentences and psychiatric examinations for sex offenders. It opposed a bill for the licensing of chiropractors. It took an active part in advocating legislation which would have made possible the utilization of unwanted dogs for medical research. It favored a bill for a year's study by a legislative committee of the problems of alcoholism.

The enumeration of these items give you some indication of the amount and importance of the work performed by the Committee on Public Health Relations with Dr. George Baehr as its Chairman and Dr. E. H. L. Corwin as its Executive Secretary.

The Committee on Medicine and the Changing Order has continued to hold a watching brief during the year. It has viewed with satisfaction the gradual implementation of the recommendations made in former years on the ways and means of making available to a larger and larger public all that modern medicine can provide. It hails the ever-increasing enrollment in voluntary health insurance plans and the growing enlightenment of the public as to their value as opposed to compulsory national health insurance. In this matter of informing and building up public opinion the medical profession has taken a forward step.

We recognize that our profession, along with other professions and callings, must conform in its practices to an over all pattern of national policies and that it must fit into the general economic and social picture. What most of us object to is that the profession of medicine which stands so high in accomplishment; which has been making such spectacular progress in scientific research and in its application for the benefit of the whole population, should have been singled out as the stalking horse for an adventure into the dangerous and largely unexplored realm of state socialism and bureaucratic control.

The New York Academy of Medicine throughout its one hundred years of existence has ever had before it one great aim, the promotion of medical education and research to the end that it should be applied in the best possible way for the benefit of the individual and of the people at large. The Academy has moved with the times. It has never been static. It recognizes that changing conditions call for new methods of meeting them and it stands ready today as it has in the past to explore and to advise on every new approach to the problem of national health. The

comprehensive character of its fellowship fits it for this task and the objectivity of its approach to every investigation it has ever conducted is a guarantee that the problem will be thoroughly and fearlessly explored.

The Library, our most precious possession, continues to cater to a great number and variety of readers, about half of whom are other than doctors of medicine. This large lay reading public might be further increased were it more generally known that, in coöperation with the public library system of New York City, the Library is free to all. Explanatory circulars to this effect have recently been distributed to other libraries and to interested individuals. Whilst ours is thus a free public library its whole expense is borne by the Academy. Expenditures have risen steadily year by year owing to the increasing number of books published and their augmented price, together with rises in salaries and other costs of administration. A library must always continue to expand. The Committee on Library and Dr. Howard Craig have been studying ways and means of adding to the stacks and of providing better working space for staff and readers. To meet all of this it is very necessary that we seek new sources of income, a drive for which is contemplated in the coming year. In this we must enlist all of our Fellows.

We acknowledge the generosity of those who in the past year, under the auspices of the Friends of the Rare Book Room have donated valuable volumes of historical interest, the acquisition of which would ordinarily be out with our budget limits. An important working acquisition was a set of 209 volumes of the Library of Congress Catalogue of Cards, the greatest of American Bibliographies. Its very considerable cost was met by members of the Committee on Library personally and through their friends.

A new departure has been an experiment in library coöperation. Late in 1949 the Academy Library initiated a series of consultations between the librarians of seven New York institutions concerned with the literature of psychoanalysis in the hope that a survey might show possibilities of economising on purchases by minimising duplication and at the same time increasing representation of the literature. This whole enterprise constitutes what may be the first attempt at a working coordination among libraries by a partial pooling of their resources to provide less costly and yet wider service. The idea originated with Miss Janet Doe, our librarian, who has made herself responsible for working out the details. I pay tribute to her for the very efficient way in which

she administers this and all our other library activities. She and her associates have arranged a variety of exhibitions during the year such as that of Atlases of Anatomy published up to the year 1700; all of the literature bearing on cortisone and ACTH; an exhibit on "The Effects of Atomic Weapons."

Of considerable local interest was the showing of books written by New York City physicians issued in 1949; its sixty-nine titles (to which several more were added in the course of the exhibit) represent, according to Miss Doe, some 15 per cent of the medical books published in the United States in 1949, and are a crude index of the amount of work New York physicians are doing. Such an output reflects the fact that New York has become an outstanding medical center.

In 1950 The New York Academy of Medicine itself has published four volumes—The Biological Foundations of Health Education; The Social and Biological Challenge of the Aging Population; The Pathogenesis and Pathology of Viral Diseases. The first two are the transactions of the Eastern States Health Conferences of 1948 and of 1949 held under the auspices of the Committee on Medical Information and the third, edited by Dr. John G. Kidd, is the work of the Section of Microbiology. The fourth volume entitled "The Future of Medicine" incorporates the Laity Lectures of the 1949-50 Season.

Over all the activities which I have mentioned and many others the Council has kept a watchful and directing eye as has the Board of Trustees over our finances. To the latter and especially to its Finance Committee we are much beholden for the management of our invested funds. As these amount to over six million dollars this is a great responsibility. That their planning and administration have been wise is evidenced by the fact that in the last year as in the two years previously, we have lived within our income. Credit for this must also be given to our Director, Dr. Howard Reid Craig, who scrutinises all expenditures and manages to make ends meet, not only without loss of efficiency but indeed with an ever-increasing expansion of our services.

On behalf of the whole Fellowship I tender to Dr. Craig and the other Officers, to the Council and to the Trustees our sincere thanks. On my own part I wish to convey to them my gratitude for the innumerable ways through which they have contributed to making my term as President one of the happiest, most rewarding, and most memorable epochs in my life.

SOME RECENT ADVANCES IN THE STUDY OF URIC ACID METABOLISM AND GOUT*

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GOUT may be defined, for our present purpose, as a disorder of purine metabolism characterized by hyperuricemia and a typical form of recurrent acute arthritis, often eventually associated with urate deposits in cartilage, joint spaces, bursae, tendons, kidneys and other tissues, these deposits sometimes becoming manifest clinically as tophi or in roentgenograms. The natural history of gout is generally divided into two phases, which may overlap: "acute gout," the initial and often only phase characterized by recurring attacks of acute gouty arthritis with virtually complete freedom of symptoms between attacks; and "chronic gouty arthritis," the later phase when the intervals between acute attacks no longer are symptom-free but are characterized by progressive disability due to stiffness and deformities of joints, by the appearance of tophi and by typical roentgenographic changes.

The clinical manifestations of gout have been extensively studied and we have fine descriptions of the disease, in this country notably by Talbott,[1] Bauer and Klemperer,[2] Hench,[3] and others. In recent years the hereditary aspects of gout have been subjected to analysis, for example in the studies of Talbott,[4] Smyth et al.,[5] and Stecher et al.[6] Methods for the more specific determination of uric acid in serum and urine have been developed, particularly through the introduction of the use of uricase in serum by Blauch and Koch[7] and in urine by Buchanan, Block and Christman.[8] The management of gout, too, has made great strides, largely through the rediscovery of colchicine and other happy empirical accidents.

But despite all these advances, we still have little insight into the

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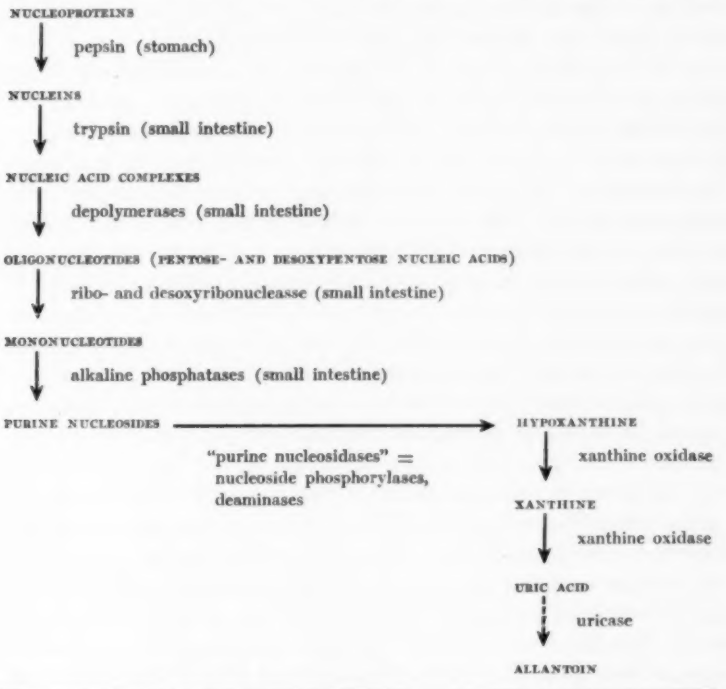
** Now at Mount Sinai Hospital, New York.

Fig. 1. DERIVATION OF URIC ACID FROM INGESTED PREFORMED NUCLEOPROTEINS.



fundamental nature of the underlying metabolic error in gout and most of the basic problems posed by the disorder have resisted all the efforts of classical biochemical investigation. Only in very recent years, with the introduction of new techniques particularly in the employment of isotopes, has some progress in this direction been made and the way to further elucidation opened.

It is the purpose of this presentation to summarize some of these advances, particularly in relation to uric acid metabolism, and to point out wherein they have implications for the clinical problems of gout or, when these are not yet evident, what may be their future signifi-

cance. To indicate how the management of gout already has been influenced by these developments I shall also outline current lines of thinking and experiment in prophylaxis and therapy.

The scheme in Fig. 1 reflects the classical concept of the derivation of uric acid from ingested preformed nucleoproteins. In the stomach these are degraded by pepsin to nucleins, protein-nucleic acid complexes of variable composition. Hydrolysis by trypsin in the small intestine first yields nucleic acid macromolecules which are then depolymerized to oligonucleotides, first to pentose- and desoxypentose nucleic acids and by specific ribo- and desoxyribonucleases in the small intestine to mononucleotides. Dephosphorylation by the alkaline phosphatases of the intestine then occurs and the bulk of the resulting purine nucleosides are acted upon by a variety of "purine nucleosidases" and deaminases to form hypoxanthine. By the action of xanthine oxidase, hypoxanthine is oxidized in the #2 carbon position to xanthine and then in the #8 carbon position to uric acid. In most mammals uric acid is further degraded by uricase to allantoin but human tissues appear to be devoid of uricase and the final purine product of the metabolism of nucleic acid in man is uric acid.

This series of reactions leading to the formation of uric acid, recently admirably reviewed by Schlenk,[9] is, of course, of great importance from the point of view of gout. Of special interest, perhaps, are the complex enzymatic processes involved in the transformation of the purine nucleoside precursors of uric acid to hypoxanthine and I should like to speculate for a moment about their possible significance in relation to acute gout. Ever since Wollaston and Garrod called attention to the excessive uric acid in gout the association of these two phenomena has largely dominated clinical thinking about gout. There can be no question that the manifestations of chronic tophaceous gout are due to deposition of urate in the tissues. The tacit assumption that acute gouty arthritis also is due to uric acid per se is, however, open to serious doubt, I believe. From all indications, uric acid is a physiologically inert substance quite incapable of producing the dramatic changes of acute gout. Uric acid fed by mouth, injected by vein or injected into joints or tissues will not cause an acute attack of gout either in the normal or gouty subject. Many individuals with marked and sustained hyperuricemia due to various causes (chronic renal insufficiency, for example) go along indefinitely without acute gout. In the gouty pa-

tient it is a common clinical observation that acute gout usually involves joints that do not give evidence of large urate deposits in roentgenograms, and as more and more urate is deposited in and around that joint the acute attacks are apt to migrate to other joints as yet relatively free of urate deposits. There is no consistently significant change in the serum level or urinary excretion of uric acid just prior to, during or following an untreated acute attack of gout, nor are any significant changes in these levels associated with remission induced by colchicine. Uricosuric agents (except ACTH and cortisone) do not convincingly prevent or abate acute attacks of gout in spite of the marked increase in urinary excretion and decline in serum uric acid they produce; in fact, we have on several occasions encountered apparent precipitation of acute gout in association with vigorous uricosuria. In the case of ACTH or cortisone no correlation can be made out between the uricosuric effect and the degree of clinical response—marked uricosuria may be produced with little or no amelioration of symptoms. In short, it seems more reasonable to suppose that acute gouty arthritis is evoked by some precursor of uric acid, as yet unidentified, than by uric acid itself.

In the enzymatic conversion of purine nucleosides to hypoxanthine an interesting and important development is the demonstration by Kalckar [10, 11] of phosphorolysis of ribose and desoxyribose nucleosides by the action of specific nucleoside phosphorylases, with the formation of ribose-1-phosphate and desoxyribose-1-phosphate respectively. The reactions are analogous to the phosphorylation of glycogen and glucose which play so important a role in our current concepts of carbohydrate metabolism and diabetes; perhaps phosphorylation of nucleosides may prove to have some relation to gout.

These are mere speculations. Certain it is, however, that another recent advance in our knowledge of uric acid metabolism, a major triumph of the application of isotope techniques to biological problems, has direct bearing upon the basic mechanisms of gout: the demonstration that uric acid is synthesized in the body at a lively rate from the simplest carbon and nitrogen compounds. For this contribution we are indebted particularly to Barnes and Schoenheimer,[12] Buchanan, Sonne and associates,[13, 14] Shemin and Rittenberg,[15] Karlsson and Barker,[16] and Elwyn and Sprinson.[17] It is now established that dietary ammonia is readily incorporated into the uric acid molecule, directly or via the

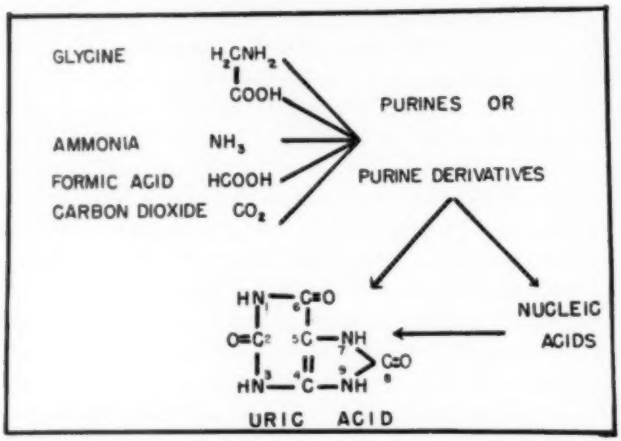


Fig. 2. Biosynthesis of uric acid.

general nitrogen pool. Glycine contributes to the formation of uric acid, being incorporated chiefly into the 4, 5 and 7 positions of the uric acid molecule (Fig. 2). The ureide carbon atoms #2 and #8 are derived from the carbon of formate, which may, in turn, be derived from the *a* carbon of glycine and *β* carbon of serine. Since serine is (reversibly) converted to glycine and formate, serine also is a direct precursor of uric acid. Carbon atom #6 of the uric acid molecule is derived by carbon dioxide fixation.

Fig. 2 summarizes this recent expansion of the classical concept of the origin of uric acid as expressed in Fig. 1. It will be noted in Fig. 2 that prior incorporation of uric acid precursors into nucleic acids is not an obligatory step in biosynthesis but that direct conversion to uric acid may occur. A possible intermediate is 5(4)-amino-4(5)-imidazole-carboxamide (Fig. 3), first isolated from sulfonamide-treated E. coli cultures by Stetten and Fox[18] and subsequently identified by Shive and associates.[19] The probability that this substance actually may be an intermediate in uric acid biosynthesis was enhanced considerably by the recent demonstration by Schulman, Buchanan and Miller[20] of its conversion to hypoxanthine when incubated with pigeon liver homogenate.

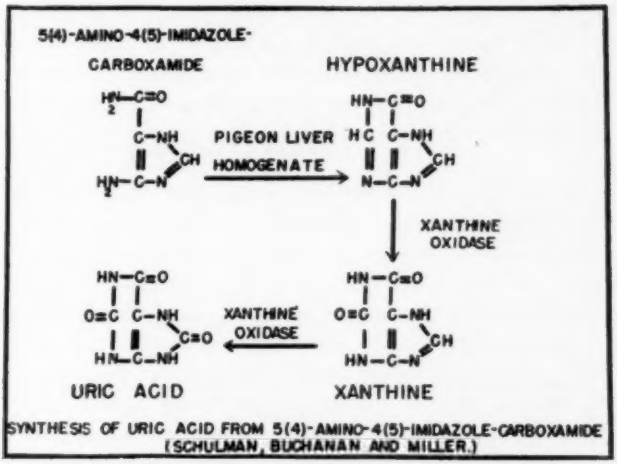


Fig. 3. Scheme for uric acid formation from 5(4)-amino-4(5)-imidazole-carboxamide.

It is apparent from all these developments that dietary proteins, fats and carbohydrates all are potential precursors of uric acid and must therefore be taken into account in any consideration of the dietary regulation of gout. The amount of uric acid formed in the body depends not only upon the intake of preformed purines but, as pointed out by Shemin,[21] "upon the rate of formation of the purines from their precursors, the availability of the precursors, the amount of direct oxidation of the formed purines, the turnover rates of the pentose nucleic acids of different cells and the rate of regeneration of the cells."

This brings us to another important discovery, the development by Stetten and associates[22-24] and by Brown and associates[25] of isotope techniques for estimating in the normal or gouty subject the size of the miscible pool of uric acid (i.e., the amount of uric acid present in the body in a form capable of prompt mixing with intravenously injected N^{15}-labeled uric acid) and the rate of its turnover. When, following injection of labeled uric acid, the concentrations of N^{15} in the urinary uric acid are plotted against time on semilogarithmic coordinates, a straight line is obtained (Figs. 4 and 5) whose slope of decay is equivalent to

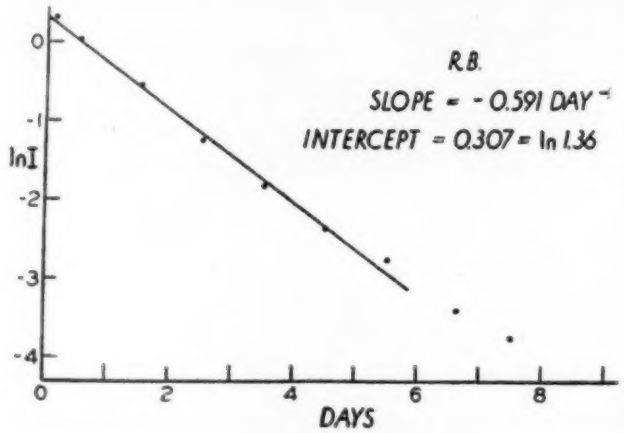


Fig. 4. Decay curve, N^{15}-labeled uric acid following injection into normal subject (from Benedict, Forsham and Stetten[25]).

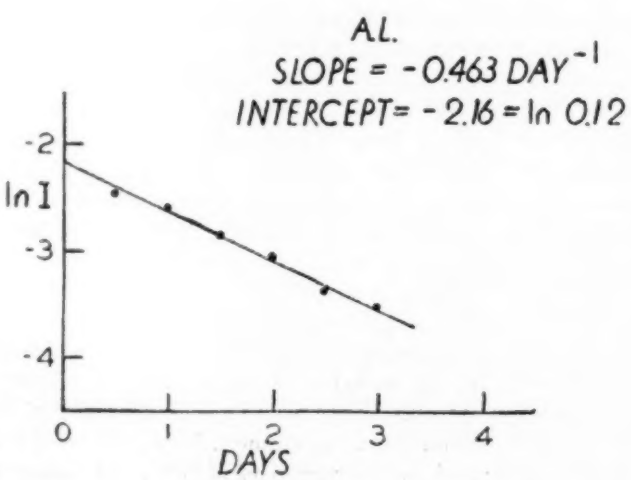


Fig. 5. Decay curve, N^{15}-labeled uric acid following injection into gouty subject (from Benedict, Forsham and Stetten[25]).

the proportion of the miscible pool daily replaced by newly formed uric acid. From the extrapolated intercept (the logarithm of the excess N^{15} concentration of the miscible pool at the time of initial mixing), and the quantity and isotope concentration of the injected uric acid, the magnitude of the miscible pool can be calculated. The turnover rate of the pool is computed from the quantity of the miscible pool and the slope of the line of decay.

The method involves certain assumptions the validity of which, particularly in gouty patients with large tophaceous deposits and impaired renal excretion of urate, has not yet been established. Moreover, the morphological limits of the miscible pool, particularly in respect to urate in the solid phase, have not been clearly defined although it is established that large, solid tophi take up very little of the injected isotopic uric acid. Nevertheless, this technique has already given new insight into various aspects of the problem of gout and affords first approximations of quantities and rates of formation of uric acid that have hitherto defied analysis. It has been shown that in normal man a pool of about 1.2 Gm. of miscible uric acid is present in the body and that 50-75 per cent of this quantity is daily replaced by newly formed uric acid. In gouty subjects the miscible pool of uric acid is increased, as much as fifteen-fold in one advanced case of tophaceous gout, and can be depleted by protracted administration of uricosuric agents. It has been possible to establish the presence of markedly increased deposition of urate not clinically or roentgenographically demonstrable; it is apparent that many patients with gout are slowly accumulating potentially crippling urate deposits not yet manifest as chronic gouty arthritis or tophaceous gout, a point which has a direct bearing on the philosophy of management of gout. Additional evidence has been provided by this method that uric acid is not degraded to any significant extent in man, although it must be admitted that the estimated rate of production of uric acid in normal man greatly exceeds the daily output in the urine and the difference is not accounted for except perhaps by excretion of unexpectedly large amounts into the gut and breakdown there by the bacterial flora. Whether or not the rate of production of uric acid is excessive in gout, a crucial point, has not yet been established. Studies in this direction are now in progress.

The role played by the kidneys in gout has been a controversial question for many years and one that is still not resolved. A major

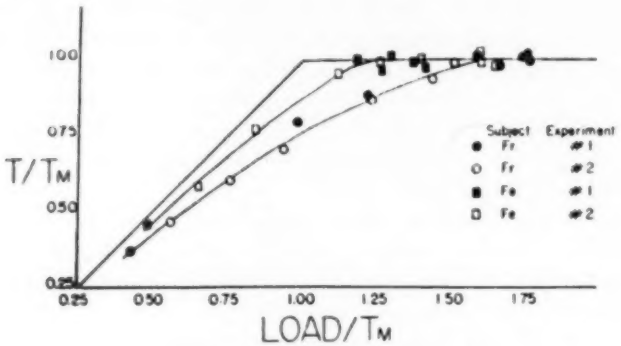


Fig. 6. Relationship between urate load and urate reabsorbed (from Berliner et al.[26]).

difficulty is that the normal renal mechanisms for regulation of urate excretion remain obscure. Recently, however, a large stride toward elucidation of these mechanisms was made by Berliner and colleagues[26] who applied modern methods for the study of discrete renal functions to this problem. Their data are consistent with the view that virtually all the urate in plasma is in filterable form, at least in normal man; and that the amount of urate filtered therefore approximates the product of glomerular filtration rate (as measured by inulin clearance) and the plasma urate concentration: 5 or 6 mg. of urate filtered per minute. About 10 per cent of this amount normally appears in the urine. Investigating the nature of tubular mechanisms for reabsorption of urate by continuous intravenous infusion of uric acid, it was found that, at first, as the amount of urate filtered increased the amount reabsorbed also increased; but when the filtered load reached approximately 15 mg. of urate per minute no greater urate reabsorption occurred (Fig. 6). Thus a maximum tubular transport capacity, Tm, was established for uric acid in normal man, indicating "active" (enzymatic) tubular transport. The capacity of this mechanism is so large, however, that it is not exceeded in the normal individual and probably not in the gouty subject. The factors which actually determine the amount of urate excreted under normal circumstances and in gout are still unknown.

The amount of uric acid excreted in gout, in relation to the normal excretion, is an important point for our understanding of the disorder

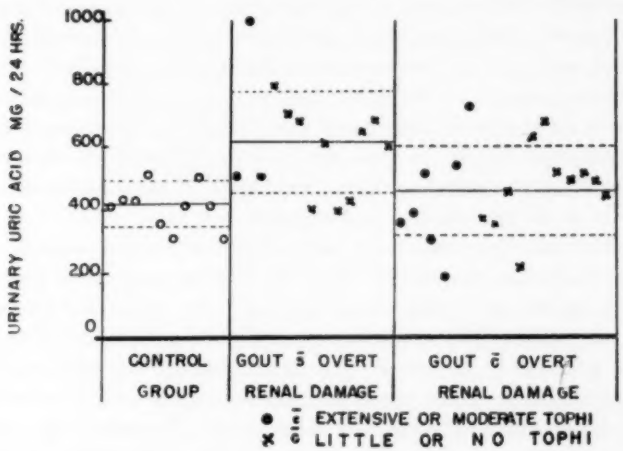


Fig. 7. Comparison of urinary uric acid excretion in non-gouty subjects, gouty subjects without overt renal damage, and gouty subjects with overt renal damage. In each category the solid line represents the mean, the broken lines indicate standard deviation. Solid dots represent cases with extensive tophaceous gout, crosses represent cases with few or no tophaceous deposits (from Yü[31]).

but surprisingly few data are available and the issues involved have been obscured by more or less tangential interests. The literature on gout implies that the urinary uric acid excretion of the gouty subject is usually within normal limits and is often depressed. This is probably true but the significant fact remains that some patients with gout excrete excessive amounts of urate.[27, 28] Brøchner-Mortensen[29] found a mean urinary uric acid excretion of 414 mg. per day (range 297 to 680 mg. /day) in eleven gouty subjects as compared with a mean of 374 mg. per day (range 269 to 532 mg./day) in twenty normal persons. Friedman and Byers[30] obtained a mean figure of 567 mg. uric acid per day (range 472 to 613 mg./day) in five relatively young patients with gout and a mean of 390 mg. per day (range 360 to 438 mg./day) in six normal subjects. Yü[31] found a mean urinary uric acid excretion of 523 ± 169 mg. per day in thirty-one gouty patients as compared with 424 ± 73 mg. per day in ten non-gouty control subjects. All subjects were maintained on a low purine, low protein diet. In thirteen of Yü's gouty patients with apparently unimpaired renal function as indicated by

serum NPN, PSP excretion test and routine urine analysis, the mean daily urinary excretion of urate was 614 ± 162 mg.; in eighteen gouty subjects with more or less overt renal damage the mean daily urinary excretion of urate was reduced to 457 ± 143 mg., not significantly different from that of the control group (Fig. 7). The nature of the frequent renal damage in gout was recently reviewed by Brown and Mallory[32] in connection with the occurrence of nephrosclerosis, urate deposits in the medulla and pyelonephritis.

Unfortunately, satisfactory data on fecal excretion of uric acid are not available. Geren, Bendich, Bodansky and Brown[25] recently demonstrated by use of isotope-labeled uric acid that when fed by mouth uric acid is extensively oxidized to urea and ammonia in the alimentary tract, presumably by uricase and allantoinase of the bacterial flora.

With all these recent advances in mind we are now ready to examine the present status of a fundamental problem of gout: Is the hyperuricemia characteristic of the disorder due to increased production, decreased destruction or impaired renal excretion of uric acid? As indicated, no definitive answer can yet be given. It can be said, however, that excessive urinary uric acid excretion in some patients with gout indicates endogenous overproduction of uric acid in at least these instances and this should be regarded for the present as a primary factor; that impaired renal excretion of uric acid is an important but probably usually secondary factor which in many cases contributes significantly to hyperuricemia, particularly in the later phases of gout; and that significant degradation of uric acid in man has not been demonstrated except by the bacterial flora of the intestinal tract. Chronic gout, whether or not accompanied by manifest tophi or persistent arthritis, is associated with more or less deposition of urate, the result of a rate of formation of uric acid in excess of the rate of elimination. These views are necessarily only tentative but it may confidently be expected that with the techniques now available more secure answers will soon be found.

The greater insight obtained through all these advances in our knowledge of the metabolism of uric acid and its precursors has already distinctly influenced thinking and experiment in the management of gout.[33] For example, in respect to regulation of diet, always a very controversial subject, it is now clear that since not only preformed purines but also all proteins, carbohydrates and fats must be regarded

as potential precursors of uric acid, absolute control of urate formation by dietary restriction of the gouty subject is impossible. Nevertheless it seems prudent to attempt to minimize the rate of uric acid production, at least in patients with chronic gouty arthritis and in those subject to frequent recurrences of acute gout. The most feasible approach would seem to be restriction of nitrogen, in the form of proteins as well as purines, and for several years I have been using diets limited to dairy products, cereals, eggs, non-leguminous vegetables and fruits in such cases. The results are inconclusive. Attacks of acute gout may occur in spite of rigid dietary restriction alone although I have the distinct impression that they may diminish in frequency and intensity. In chronic gouty arthritis there appears to be less stiffness and disability and most of my patients have voluntarily continued to adhere more or less closely to their onerous diet on that account. This kind of evidence is unsatisfactory, however, and it is to be hoped that the new isotope techniques will make possible more precise measurement of the effects of diet, at least on the size of the miscible pool of uric acid.

In the treatment of acute gouty arthritis the mainstay of therapy is still colchicine, which is given in divided doses usually to the point of diarrhea, nausea or vomiting. There is a growing conviction that colchicine also has a preeminent place in the *prophylaxis* of acute gout when there is frequent recurrence of attacks. In our experience in twenty-four such cases the regular ingestion of colchicine, in conjunction with dietary restriction of proteins and purines, has proved to be by far the most effective method of minimizing the frequency and intensity of acute gouty attacks; in some instances this has made the difference between virtual incapacitation and relatively normal activity. The patients regularly take colchicine, usually every night or every other night in doses of 0.5 or 1.0 mg., occasionally more in very severe cases, according to their individual requirement. They are taught also to take larger abortive doses of colchicine upon the first intimation of an attack when there is warning pain, stiffness or other indisposition. Adjuvant analgesics, particularly salicylates, are employed especially when residual stiffness of joints is present.

We now have two other effective agents in the treatment of acute gout, ACTH in divided daily doses of 50-100 mg. and cortisone in doses three or four times that amount. ACTH may be rapidly effective in the occasional patient who responds slowly and incompletely to

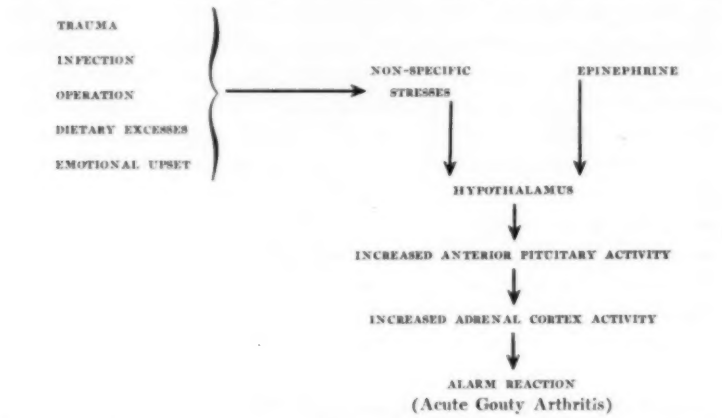


Fig. 8. Theory of role of so-called pituitary-adrenal axis in precipitation of acute gout

colchicine; on the other hand, this agent may be ineffective in patients who do well with colchicine, as in four of eleven cases in our experience.[34] Although exacerbation of acute gout may occur a day or two after remission induced by ACTH or cortisone,[35] this has seemed in our patients to be attributable to inadequate or insufficiently prolonged administration of these agents; and we have been able to induce an acute attack in interval gout by abrupt cessation of full doses of ACTH only once in eight attempts.[34] Wolfson and others are now treating acute gout with both colchicine and ACTH or cortisone, continuing administration of colchicine indefinitely or for some time after the acute symptoms have subsided in order to prevent recurrences.

There has been some disposition to interpret these effects of ACTH and cortisone quite literally as indicating that gout is essentially a disease of the so-called pituitary-adrenal axis. Hellman[35] has suggested the interesting idea that the various precipitating causes of gout such as trauma, infection, operation, dietary excesses, emotional upsets, etc., are in effect non-specific stresses which elicit an alarm reaction taking the form, in the individual predisposed to gout, of acute gouty arthritis. The sequence of events, according to this theory, may be pictured

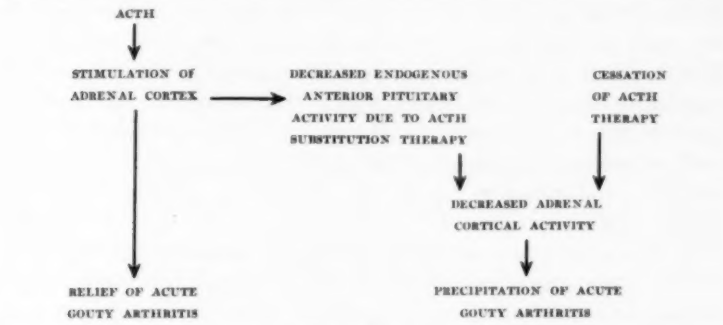

ACTH
STIMULATION OF ADRENAL CORTEX
DECREASED ENDOGENOUS ANTERIOR PITUITARY ACTIVITY DUE TO ACTH SUBSTITUTION THERAPY
CESSATION OF ACTH THERAPY
DECREASED ADRENAL CORTICAL ACTIVITY
RELIEF OF ACUTE GOUTY ARTHRITIS
PRECIPITATION OF ACUTE GOUTY ARTHRITIS

Fig. 9. Postulation of action of ACTH in both alleviating and precipitating acute gout.

as in Fig 8.* This scheme would not readily account for the striking therapeutic effect of ACTH and cortisone in acute gout without having to make further speculations so a more general scheme (Fig. 9)* has been proposed by others to account for the dual termination and precipitation of acute gouty arthritis ascribed to ACTH. An abnormal adrenocortical androgen and imbalance in secretion of various 11-oxysteroids have also been postulated in gout by Wolfson[36] to account for the absence of androgen deficiency in gouty subjects showing diminished urinary excretion of 17-ketosteroids. As indicated elsewhere[34] the evidence presented for these views does not thus far seem compelling. The diversity of diseases favorably affected by ACTH and cortisone is so extraordinary that it is stretching all credulity to believe that these agents act in each instance upon a different primary causal mechanism, including that of gout—it seems more rational to assume an effect through some peripheral tissue response common to a wide variety of diseases. Moreover, gout does not occur spontaneously in the various disorders of the anterior pituitary or adrenal glands associated either with hypo- or hyperfunction. Finally, certainly in the instance of colchicine there is no warrant for the assumption of a therapeutic effect through the pituitary-adrenal axis.

Returning to management, the slow and insidious development of

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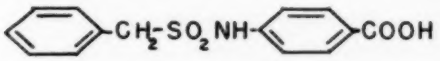
tophaceous deformity and crippling arthritis of chronic gout has received far less critical attention than the prevention and treatment of the more spectacular manifestations of acute gout. The problem in chronic gouty arthritis is to minimize the deposition of urate and, if possible, to mobilize such deposits once formed. Two methods of attack are available, first to restrict the diet so as to reduce the intake of uric acid precursors, an approach which has the severe limitations already indicated; and second to increase the excretion of urate by the use of suitable uricosuric agents. It should be noted in this connection that control of acute gouty attacks by the regular administration of colchicine does not appear to prevent the steady deposition of urate in the tissues, since colchicine has no significant effect on urinary uric acid excretion, in our experience. We have six patients who were maintained tolerably free of acute gouty attacks over a period of five to thirteen years by the regular use of colchicine but nevertheless developed marked chronic tophaceous gout during this period.

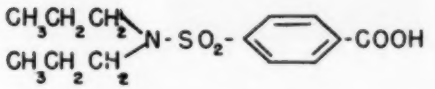
As has long been known, salicylates effectively increase urinary uric acid excretion, particularly when combined with alkalinizing agents such as sodium bicarbonate. Dr. Yü and I found, however, that when salicylates are administered the determination of uric acid in the urine, even with the use of uricase, is subject to appreciable positive error due to the appearance in the urine of an oxidation product, gentisic acid, which gives as much color with uric acid reagents as does uric acid itself.[37] Even with corrections for this error, we found that the urinary excretion of "true" urate is markedly increased when sufficiently large doses of salicylates are used. Thus, the mean increase in urinary "true" uric acid excretion (corrected for gentisic acid and other nonurate chromogens) in seven gouty patients given 1.3 Gm. acetylsalicylic acid 4.i.d. together with 5.0 Gm. sodium bicarbonate daily was 79 per cent. This was associated with a sharp drop in serum uric acid. Smaller doses of aspirin, such as 3.0 Gm. daily, were found to have no significant uricosuric effect in most patients. These results substantiate in all essentials the findings of Jennings,[38] Bauer and Klemperer[39, 40] and Robinson and Block.[41] Unfortunately, however, only one of our patients could tolerate the required large dosage of aspirin for more than a few consecutive days since in the older age group represented tinnitus, confusion, gastrointestinal symptoms and other indications of salicylism soon supervene.

CARINAMIDE



4'-CARBOXYPHENYLMETHANESULFONANILIDE

BENEMID



P-(DI-N-PROPYLSULFAMYL)-BENZOIC ACID

Fig. 10. Structural formulas of the uricosuric agents Carinamide and Benemid.

On the basis of a report by Wolfson and associates[42] that carinamide increases urinary uric acid excretion in normal subjects, our attention was then directed to carinamide and Benemid* (Fig. 10), two drugs developed for use with penicillin or para-aminosalicyclic acid to maintain higher antibiotic blood levels.[43] On a daily dosage of 12-13.5 Gm. carinamide, the mean increase in urinary urate excretion in thirteen gouty patients was 61 per cent, associated with a marked and sustained decline in the serum uric acid level. Administration of carinamide could be maintained for weeks or months but the large number of tablets consumed daily was objectionable and although the drug is of low toxicity,[44] a variety of reactions—gastrointestinal symptoms, drug fever, drug rash—developed in some cases. Benemid in divided daily doses of 2.0 Gm. produced a mean daily increase in urinary uric acid excretion of 58.5 per cent in 14 gouty patients. This was associated with a sustained fall in serum uric acid to approximately half the initial level (Fig. 11). Reactions to protracted administration were of the same character as with carinamide but were less marked and

* We are indebted to Sharp and Dohme for a generous supply of this drug.

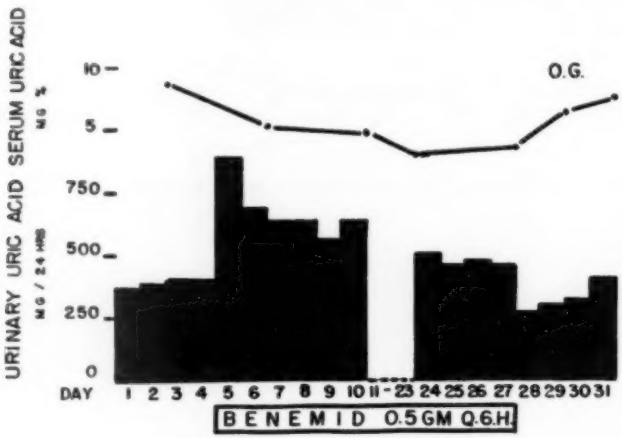


Fig. 11. Uricosuric action of Benemid in a patient with chronic gout. Administration of Benemid, 2.0 gm. daily, was begun on the fifth day and continued through the twenty-seventh day of observation. Note sharp increase in urinary uric acid excretion and fall in serum uric acid level.

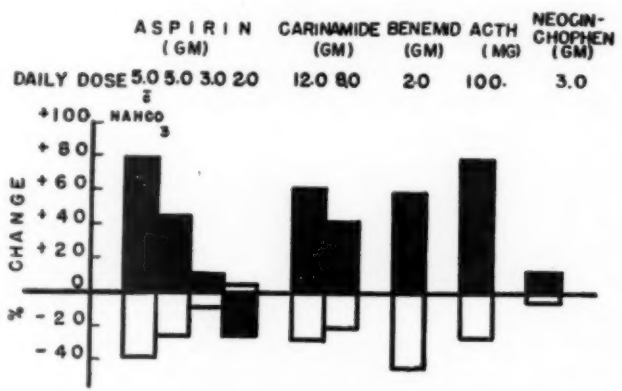


Fig. 12. Comparison of mean effects on urinary uric acid excretion and serum uric acid level of aspirin 5 gm. daily combined with 5.0 gm. sodium bicarbonate; aspirin alone 5 gm. daily; aspirin 3.0 gm. daily; aspirin 2.0 gm. daily (retention of uric acid); Carinamide 12.0 gm. and 8.0 gm. daily; Benemid 2.0 gm. daily; ACTH 100 gm. daily; Neocinchophen 3.0 gm. daily.

frequent except for an apparent propensity to provoke acute gout in four patients who required covering doses of colchicine. Smaller doses of 1.0 Gm. daily are also effective and produce very few reactions. Thus far in our experience Benemid appears to be the most satisfactory uricosuric agent for protracted administration in chronic gout, largely in prevention of disability due to arthritis and tophi since we have as yet seen little evidence of the disappearance of established tophi. From present indications its usefulness as a uricosuric agent depends upon effective and fairly selective suppression of tubular reabsorption of urate. Benemid has no analgesic effect and is without value in the treatment of acute gout.

Fig. 12 gives a comparison of the effects on urinary uric acid excretion of the various uricosuric agents tested by us thus far.

An interesting phenomenon associated with the use of these uricosuric agents is that, except in advanced tophaceous gout, the increased urinary uric acid excretion effected gradually comes to a halt after weeks or months and control pre-treatment levels are resumed in spite of continued exhibition of the drug. This phenomenon was noted by Bauer and Klemperer[2] in connection with the protracted use of salicylates and was explained as due to acquired tolerance to the drug. An alternative concept now seems more likely. It will be recalled that Stetten[22] found that the miscible pool of uric acid, normally about 1.2 Gm., is increased in gout. It would be expected therefore that depletion of the miscible pool of uric acid by uricosuric agents would occur relatively soon in normal subjects but would require considerably more time in gout, particularly in tophaceous gout. This is precisely what Dr. Yü and I have observed. In non-gouty subjects on a constant low protein, low purine diet a distinct uricosuric effect is maintained for only a few days and the total excess uric acid mobilized is of the order of 1.0 Gm., in good agreement with Stetten's figures. In non-tophaceous gout marked uricosuria is maintained for several weeks and the total excess mobilizable uric acid over this period usually is of the order of 4-10 Gm.; some patients with early gout, however, excrete no more than the normal excess of uric acid. In advanced tophaceous gout markedly increased urinary uric acid excretion above control pre-treatment levels persists for many months; in one instance we have mobilized 75 Gm. of uric acid over a five month period, the uric acid excretion in excess of that expected on the basis of pre-treatment levels.

Summary and Conclusions

The fundamental nature of the underlying metabolic error in gout is not known but recent advances, particularly through the use of isotopes, have given more insight into the disease mechanisms.

The enzyme reactions involved in the degradation of ingested preformed nucleoproteins to uric acid have been clarified, especially by introduction of the concept of phosphorolysis of ribose- and desoxyribose nucleosides. It has been shown that uric acid is synthesized in the body at a lively rate from the simplest nitrogen and carbon compounds namely ammonia, glycine, serine, formate and carbon dioxide, and is derived not only from preformed purines but from all proteins, fats and carbohydrates. A probable intermediate has been identified. Synthesis of uric acid does not require incorporation of uric acid precursors into nucleic acids.

A method based on the rate of dilution of injected N^{15}-labeled uric acid has been devised to measure the miscible pool of uric acid and the turnover rate of this pool in normal and gouty subjects; the miscible pool of uric acid is increased in gout, enormously in some cases of chronic tophaceous gout.

A maximum tubular transport capacity for uric acid has been established, about 15 mg. per minute. It has been shown that the urinary excretion of uric acid in some patients with gout is in excess of the normal, indicating overproduction of uric acid in these instances; impaired renal excretion of uric acid is an important but probably secondary factor in many cases of gout.

These advances have already influenced thinking and experiment in the management of gout. The usefulness of dietary restriction is still unestablished but it seems prudent in patients with chronic gout and frequent recurrences of acute gout to limit the purine, protein and alcohol intake. In the treatment of acute gout colchicine, ACTH and cortisone are effective; prevention by regular administration of prophylactic doses of colchicine is important in patients subject to frequent attacks of acute gout. In chronic gout several effective uricosuric agents to prevent crippling arthritis and tophaceous deformities have been developed; of these the most useful at present appears to be Benemid.

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TUMORS OF BONES AND JOINTS*

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THE tumors of the bones and of the joints make up a large and intriguing group of lesions. In their clinical investigation, the disciplines of pathology, roentgenology, and surgery converge and reinforce each other – perhaps more strikingly than in most other fields of medical practice. These tumors have been the subject of innumerable published reports, but the possibilities of additional knowledge about them, even in regard to the practical problems relating to them, still remain considerable.

In view of the variety of tumors which one encounters in connection with the bones, it seems advisable first to have in mind a very general orienting classification of them, such as is presented in the following table. This allows for the easy pigeonholing of all the possible bone tumors into a few very general categories.

GENERAL CLASSIFICATION OF TUMORS OF BONES

TUMORS DEVELOPING AS PRIMARY LESIONS IN BONES

TUMORS INVADING BONES FROM OVERLYING SOFT PARTS

TUMORS METASTATIC TO BONES

TUMORS DEVELOPING AT SITES OF PREEXISTING BONE DISEASE

TUMORS DEVELOPING AT SITES OF DAMAGE TO BONE FROM NOXIOUS AGENTS

It would obviously be impossible here to discuss fully even the first of these categories – that is, the tumors developing as primary lesions in bones. Our comments will be along the lines of general orientation, with emphasis on a few special points in each connection.

* Presented by Henry L. Jaffe October 20, 1950, in the 23rd Graduate Fortnight of The New York Academy of Medicine.

TUMORS DEVELOPING AS PRIMARY LESIONS IN BONES

The tumors primary in bones comprise, of course, benign and malignant tumors. Some of the malignant tumors (notably malignant giant-cell tumor and chondrosarcoma) usually develop out of benign ones. As to the benign ones, these include not only indubitable tumors (such as giant-cell tumor) but also some (such as osteocartilaginous exostosis), which arise through maldevelopment, and still others (such as osteoid-osteoma), which for other reasons belong only on the periphery of the tumor field. The benign tumorous lesions to be encountered in bones are many. Some (such as neurilemoma and neurofibroma) are rare. Others (such as benign chondroblastoma and chondromyxoid fibroma) have only recently been delimited as entities. The ones which we have chosen for consideration here are giant-cell tumor, benign chondroblastoma, aneurysmal bone cyst, and chondromyxoid fibroma. The primary malignant tumors of bones are considerably less numerous than the primary benign ones. In connection with the malignant ones, we shall consider only osteogenic sarcoma – the most common of them. Familiar as it is, this lesion still raises some interesting general questions relating to its definition and differential diagnosis.

Giant-Cell Tumor.—This lesion continues to be the "problem child" among the benign tumors of bone.[1] This is true even though, in accordance with recent knowledge, the term "giant-cell tumor" is generally being used rather strictly. Specifically, it is no longer being made a catch-all for various other tumorous lesions formerly included among the giant-cell tumors, albeit as variants, merely because they contain some multinuclear giant cells. The genuine giant-cell tumor remains a lesion difficult to assay in respect to its clinical behavior. In general, it can be said, however, that it very frequently recurs after any form of local therapy against it, and that instances of metastasis from giant-cell tumor are increasingly being recorded.

Whether a particular giant-cell tumor will recur cannot necessarily be predicted from the histologic pattern of the lesional tissue. Indeed, it may recur or even metastasize when the pattern is not in itself such as to create uneasiness. Thus, an occasional giant-cell tumor runs a malignant course without presenting, even in its metastases, an obviously malignant histologic pattern. However, in most cases of malignant giant-cell tumor, the stromal tumor tissue does present a sarcomatous

appearance. Sometimes this appearance is already manifest in the original local tumor, and sometimes it does not become so until after repeated local recurrence.

Altogether, the giant-cell tumor is a rather treacherous lesion, in regard to which the term "benign," still often made part of its name, conveys a false conception of its potentialities. The treatment of choice for giant-cell tumor is radical surgical excision, if the lesion is in any site accessible to this form of treatment. It is not necessarily contraindicated as an initial procedure even if it should entail surgical fusion of a joint.

Benign Chondroblastoma.—The lesion which has been delimited under the name of "benign chondroblastoma of bone"[2] was, and still occasionally is, referred to as the "calcifying" or "chondromatous" variant of giant-cell tumor. Though the idea that the basic cell of the tumor is the chondroblast is certainly implied in the name "chondroblastoma," we are unwilling to commit ourselves unequivocally to this idea. At any rate, it is increasingly being recognized that the lesion is a distinctive one, to be held completely separate from giant-cell tumor of bone. Growing experience with the lesion has abolished the idea that it predilects the upper end of the humerus, but has reinforced the idea that it strongly predilects males. The treatment of choice is curettage. Growing experience seems to indicate also the possibility that, in rare instances, this tumor undergoes malignant transformation.

Aneurysmal Bone Cyst.—As a descriptive term, the name "aneurysmal bone cyst"[3] is meant to convey the idea of a sort of "blow-out" distension of part of the contour of the affected bone area as presented roentgenographically, and the fact that when the lesion is entered, the affected area is found to be largely a blood-filled cavity. The lesion seems to represent a radiologic-pathologic complex sufficiently striking to merit independent consideration. In the past, the lesion has usually been conceived as representing some variety of giant-cell tumor or else a peculiar hemangioma of bone. On the basis of its roentgenographic picture, it may also easily be mistaken for a malignant tumor. While aneurysmal bone cyst may represent a primary disease entity, one should allow for the possibility that it may have developed in consequence of hemorrhage in the course of which some established benign lesion has been destroyed. At any rate, the original lesion is probably neither a giant-cell tumor nor a hemangioma. Despite its ominous

roentgenographic appearance, the lesion is benign. Therapeutically, all that is usually necessary is to curette the wall, collapse the cyst, and, if it is large, fill the cavity with bone chips.

Chondromyxoid Fibroma.—There can be no doubt that, in the past, the lesion which we call chondromyxoid fibroma of bone[4] has commonly been included among the chondrosarcomas or even been designated as myxosarcoma. The tendency to interpret the lesion as a malignant rather than a benign tumor on the basis of its cytology is understandable. In fact, there is almost a paradoxical incongruity between its superficially ominous cytologic appearance and its benign clinical course. However, experience with the lesion will lead one to recognize that its tissue pattern as a whole permits one to state that the lesion is benign, even though one may not be able to support this statement with histologic details. Indeed, this is the kind of lesion for whose identification one has to call upon a sort of sixth sense to amalgamate a number of minute, evanescent impressions into a distinctive whole.

The treatment of choice for chondromyxoid fibroma is curettage of the affected bone area, after which no further trouble is to be expected, even if the curettement has not been thorough.

Osteogenic Sarcoma.—The use of the term "osteogenic sarcoma" to include also chondrosarcoma of bone has, to a large extent, been abandoned. Indeed, "chondrosarcoma" is now almost universally recognized as an entity distinct from osteogenic sarcoma. On the other hand, fibrosarcoma primary in bone is as yet not generally separated off from osteogenic sarcoma. However, if one defines an osteogenic sarcoma of bone as a malignant connective-tissue tumor in which the sarcomatous stroma forms osteoid and osseous tissue in the course of the tumor's growth, it follows that the connective-tissue sarcoma of bone which does not lay down osseous tissue (that is, the fibrosarcoma) should also be placed in a separate category.

Likewise bound up with this definition of osteogenic sarcoma are certain other questions relating to designation and nomenclature. In speaking of osteogenic sarcoma, one usually has in mind the cases in which the tumor begins in the medullary cavity of the affected bone site and eventually extends through the cortex and even into the overlying soft parts. In these typical cases, the sarcomatous stroma may lay down large quantities of tumor osteoid and bone (sclerosing osteogenic sarcoma) or, relatively little tumor osteoid and bone (osteolytic osteo-

genic sarcoma), or, on the other hand, show extensive hemorrhagic and telangiectatic areas (telangiectatic osteogenic sarcoma). In all these cases, the prognosis is poor, the 5-year survival rate averaging about 5 per cent and certainly not exceeding 10 per cent, and the general prognosis is not really influenced by the extent of ossification of the sarcoma or by the other pathologico-anatomic qualities just mentioned.

However, there is a form of osteogenic sarcoma which has a much higher survival rate, and which in other respects, too, stands out from those cases just delimited. This is the form which we choose to designate as "juxtacortical osteogenic sarcoma."[5] It is a rather distinctive bone-forming tumor which develops in relation to the periosteum and/or immediate parosteal connective tissue. It is a tumor which, at least at first, is merely oriented to the regional bone in the sense of starting just beyond the confines of the cortex. Ultimately, the tumor may come to erode the cortex of the regional bone and even invade the marrow cavity, but these facts may not invalidate its more favorable prognosis.

It should be noted that, as a rule, this lesion is not sorted out from among the conventional osteogenic sarcomas. It is very likely that in the Bone Tumor Registry's classification (1939) of the bone sarcomas, the categories of capsular and parosteal osteogenic sarcoma and the category of periosteal osteogenic sarcoma comprise mainly instances of what we call juxtacortical osteogenic sarcoma. Possibly, juxtacortical osteogenic sarcoma represents the parosteal counterpart of the much rarer, malignant form of myositis ossificans.

TUMORS INVADING BONES FROM OVERLYING SOFT PARTS

A tumor developing in the soft tissues overlying a bone area not infrequently comes to erode the regional bone cortex and may even break through into the marrow cavity. That this may happen in cases of juxtacortical osteogenic sarcoma has already been pointed out in connection with osteogenic sarcoma in general. When a juxtacortical osteogenic sarcoma is seen for the first time at such a late stage in its evolution, it may indeed be difficult to decide from the x-ray pictures at that stage whether one is dealing with this soft-part osteogenic sarcoma or with an osteogenic sarcoma of the conventional type which has begun in the interior of the affected bone and broken out into the soft tissues.

Fibrosarcomas developing in the soft parts adjacent to a bone may likewise come to erode the bone cortex and even invade the marrow cavity. A rapidly growing anaplastic fibrosarcoma which is found involving both soft parts and bone sometimes likewise raises the question of whether the tumor began in the bone and extended into the neighboring soft parts or vice versa. Even a rather slowly growing, well differentiated fibrosarcoma of soft parts may come to erode the neighboring bone. When it does, however, the x-ray picture generally gives the cue that one is dealing with a tumor invading the bone from the outside, since where the tumor is irrupting into the bone the latter tends to show a margin of sclerosis.

A muscle tumor, also, may erode into the bone, and we have even seen a remarkable instance in which a malignant granular cell myoblastoma growing in the back of the thigh had extensively invaded the femur. Finally, it may be pointed out that if, in a soft-part tumor encroaching upon a bone, one sees small, roundish radiopacities scattered through the x-ray picture of the part, one can be fairly certain that the tumor is a vascular tumor—most probably a hemangioma.

TUMORS METASTATIC TO BONES

An appreciable number of cases of cancer first attract clinical attention through the appearance of a destructive bone lesion which turns out to represent a metastasis. As a rule, study of a biopsy specimen from the bone lesion reveals clearly that this is a metastatic cancer, and often the site of the primary lesion can be deduced from the cytologic pattern of the metastasis. On the other hand, this pattern may be ambiguous because the cancer cells are undifferentiated. In such a case, it may even be difficult to decide whether one is actually dealing with a metastatic carcinoma or, for instance, with a malignant lymphoma of bone.

Search for the primary cancer in cases in which the presenting difficulty is caused by a metastatic bone lesion is by no means always promptly rewarded. Indeed, it is striking how often such initial clinical search fails, leaving the question of the primary lesion still unsettled. In the course of time, the clinical progress of the case may disclose the primary site. Occasionally, however, it is still clinically obscure even at the time of the patient's death, and in rare instances it may even be overlooked at an autopsy.

Why the first site of metastasis from a cancer is so often one or another bone is an interesting question. Furthermore, one wonders why, in some cases, much of the skeleton may eventually be found heavily riddled by cancer, while visceral metastases (and notably hepatic and pulmonary metastases) are entirely lacking. To explain this apparent shunting of the metastases to the bones, Batson[6] has worked out the concept of the "vertebral vein system." Specifically, injection experiments have led him to the conclusion that there is a network of valveless veins around the spinal dura mater and the vertebrae which also has cranial and body-wall connections and even connections with the veins in the walls of the blood vessels of the extremities. He holds this vertebral vein system to be an independent one, existing in addition to the already recognized caval, portal, and pulmonary vein systems but connecting with these and providing by-passes for them.

This so-called vertebral vein system is conceived as a venous pool or lake in which the flow is very sluggish and subject to arrest and even reversal. It provides a series of passage-ways by which cancer emboli can be seeded directly into the bones, by-passing the liver and lungs. In particular, Batson was able to show by injection experiments that the prostatic vein plexus can be made to drain into the vertebral vein plexus. The possibility of such a drainage path, leading to by-passing of the caval system, would explain the early and sometimes exclusive lodgement of remote metastases from cancer of the prostate in the skeleton. Also, injection of breast venules demonstrated the vertebral vein pattern by which cancer emboli from the breast can likewise, as they so often do, spread first to the bones of the trunk and skull.

TUMORS DEVELOPING AT SITES OF PREEXISTING BONE DISEASE

The development of a squamous-cell carcinoma in a sinus wall of a bone affected with chronic osteomyelitis was never common and is now hardly ever encountered. The occurrence of an exuberant mass of granulation tissue (the so-called granulation tissue sarcoma) in a bone heavily affected with chronic osteomyelitis has likewise become rare. That a sarcoma may develop in one or another affected bone in a case of fibrous dysplasia has recently come to be recognized,[7, 8] but the incidence of this complication seems to be very low.

In connection with Paget's disease of bone, however, tumor development in affected bones is not at all unusual, though its actual incidence

is not clearly established. One can rate the incidence of this complication as being between 5 and 10 per cent among those cases in which the skeleton is heavily involved. However, one must not lose sight of the fact that it is found occasionally even when the Paget's disease is of rather limited extent.

The tumor itself is not necessarily a bone-forming sarcoma – that is, a straightforward osteogenic sarcoma. It may be of the nature of a fibrosarcoma, the tumor not infrequently being quite anaplastic and the stromal cells strikingly polymorphocellular. Occasionally, however, especially when it develops in an affected calvarium, the tumor may present the cytology of a giant-cell tumor, and furthermore even of one without ominous histologic characteristics. The development of a tumor in one bone site in a case of Paget's disease is soon followed by the appearance of tumors in other affected bone sites. This multicentric occurrence apparently represents the development of independent lesions in the various sites. In general, the appearance of a clear-cut sarcoma in a case of Paget's disease is an ominous prognostic indication. The course in those cases in which giant-cell-tumor-like lesions appear in the calvarium in single or even multiple foci seems to be much more favorable, so far as we know at present.

TUMORS DEVELOPING AT SITES OF DAMAGE FROM NOXIOUS AGENTS

In relation to the bones, there have been many clinical and experimental observations of both the immediate and remote harmful effects of the external application of roentgen and radium rays. It has been clearly established that if, for therapeutic purposes, one or more long bones, for instance, of a young child have been irradiated with too large a single dose, or at too frequent intervals, the bone or bones in question may become stunted because of damage to the epiphysial cartilage plate areas.[9] In a child, or in an adult, in whom, of course, the plates no longer exist, intensive external radiation is known to induce injury to the other bone elements also. That is, it may damage the periosteum, bone marrow, spongy bone, and cortex. The complex of changes which may appear under these conditions is usually designated as "radiation osteitis."[10] Specifically, this involves necrosis and sclerosis of the osseous tissue and fibrosis of the bone marrow. The bones so affected also become brittle and highly susceptible to fractures (which are also slow in uniting) and to infection.

That a sarcoma may develop in a bone which has been heavily irradiated has become increasingly evident as experience accumulates.[11, 12, 13] There is quite likely to be a lag of five years or so between the time of the intensive radiation and the appearance of the malignant tumor. The latter has been known to develop in a bone which had been heavily irradiated in the treatment of an infection (tuberculosis, for instance), a non-malignant tumorous bone lesion (such as a giant-cell tumor or a bone cyst), and even in an originally sound bone which had been within the field of irradiation. Though the incidence of post-irradiation sarcoma is apparently not high, its occurrence can not be doubted, and should be a deterrent to irradiation of benign bone lesions which could be treated by surgery instead. These experiences are in line with the earlier observations on the development of bone sarcomas in persons who, years before, had either ingested or inhaled salts of radium or mesothorium, the salts having lodged in the bones and first induced a radiation osteitis.[14]

TUMORS OF JOINTS

When thinking of tumors of joints, one usually has in mind the tumors developing in relation to the synovial membrane. However, the tendon sheaths and bursae mucosae have linings which closely resemble the synovial membrane of joints. Hence, it is not surprising that entirely analogous lesions should develop in the lining membranes of these various structures.

These lesions include the so-called "synovial sarcoma" or "synovioma." This is a relatively rare, highly malignant tumor, of specialized cytologic architecture. The histologic diagnosis of synovioma may present some practical difficulty, however, since much of the lesional tissue may show the pattern of a spindle-cell sarcoma. Thus, one may have to search the tissue to find, in the sarcomatous stroma, the characteristic clefts bordered by synovial lining cells which establish the diagnosis of synovioma.

More frequently, one encounters, in relation to the lining of articular capsules, bursae mucosae, and tendon sheaths, the lesion which has been designated as pigmented villonodular synovitis, bursitis or tenosynovitis respectively.[15] This lesion is at most only a quasi-tumor and apparently represents some local proliferative reactive process. When the villi and nodules of the lesion become matted together, as they so

often do, the cytologic pattern may be such as to invite confusion with synovioma or with some other form of malignant tumor. Safe guides in the histologic differentiation from the synovioma include the absence of a spindle-cell sarcomatous stroma and the presence of numerous phagocytes containing hemosiderin pigment and lipid which is mainly cholesterol.

In relation to clinical diagnosis, it is worth noting that, in the roentgenograph, a synovioma not infrequently presents spotty radiopacities, while the shadow cast by a villonodular lesion of large size presents a sort of lobulated configuration.[16]

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MODERN TREATMENT OF SYPHILIS*

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THE modern treatment of syphilis is relatively easy and simple. In the great majority even of late cases it can be completed within 15 days. Although I do not advise minimum therapy such as a single treatment for early syphilis, it is a fact that early darkfield positive syphilis has responded well in at least 85 per cent of cases following a single treatment with 2,400,000 units of procaine penicillin in oil and aluminum monostearate and at Bellevue Hospital we have found no advantage in continuing the treatment of most cases of early syphilis with repository preparations of penicillin beyond one week. Late neurosyphilis which was formerly the most difficult type of the infection to treat can now apparently be successfully arrested in over 90 per cent of cases by 15 daily injections of 600,000 units of procaine penicillin in oil and aluminum monostearate.

The introduction of the slowly absorbed procaine penicillin in oil and aluminum monostearate has made possible a variety of schedules for the treatment of all types of syphilis. Injections can be given daily or at less frequent intervals. For early acute syphilis three injections of 1,200,000 units of procaine penicillin in oil and aluminum monostearate given at intervals of two or three days should be sufficient therapy for 90 per cent of cases. In my opinion it is wise to give no less than 1,200,000 units for the first injection in the treatment of early syphilis. Following this initial treatment, daily injections of 600,000 units can be given for five days or injections of 1,200,000 units can be given at less frequent intervals. If desired, injections of 1,200,000 units can be spaced at weekly intervals for three or four weeks but in our experience at Bellevue Hospital there is no advantage in such prolonged therapy and I believe that more frequent injections are advisable. This

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belief is based on the as yet unexplained and possibly not significant observation that more cases of prolonged seroresistance with very low reagin titers have been observed at Bellevue Hospital when penicillin therapy of early syphilis was prolonged for fifteen days or more than when treatment was completed in eight days.

For late syphilis other than neurosyphilis a total dosage of 6,000,000 units of penicillin, given over a period of not less than ten to fifteen days, should be adequate for most cases. Injections of 1,200,000 units can be given every other day or injections of 600,000 units can be given daily with the omission of Saturdays and Sundays if the latter is desired. For all types of neurosyphilis we have found at Bellevue Hospital that daily injections of 600,000 units of procaine penicillin in oil and aluminum monostearate for fifteen days have afforded satisfactory treatment in over 90 per cent of cases. Probably injections of 1,200,000 units every other day for eight injections would give equally good results.

For relapses the total dosage of penicillin should be increased over the amounts suggested for the original treatment. Genuine relapses of patients treated for early syphilis can be treated with double the amount of penicillin advised for the original treatment but it is by no means easy to distinguish between true relapse of early syphilis and reinfection. The latter, as a rule, does not require larger total doses of penicillin than those used for the original treatment. For relapsing or very resistant cases of neurosyphilis at Bellevue Hospital we have had to retreat several patients three or four times with increasing doses of penicillin. Satisfactory results so far as the spinal fluid findings are concerned were obtained in two cases only after a third re-treatment with 40,000,000 units of procaine penicillin in oil and aluminum monostearate. In my experience, it is rarely necessary to resort to metal or fever therapy in the treatment of any type of syphilis. With possible very rare exceptions, penicillin will accomplish more than bismuth and arsenicals in all cases of relapsing syphilis. I have had very little experience with aureomycin or other antibiotics than penicillin in the treatment of syphilis but I would be inclined to try aureomycin rather than metal therapy in penicillin resistant cases.

An occasional case of penicillin sensitivity may be encountered where it is impossible to use penicillin. At Bellevue Hospital we have encountered very few such cases. The fact that a patient develops urti-

caria and angioneurotic edema during or after penicillin therapy does not mean that that patient has permanent sensitivity to penicillin. Most such cases will tolerate penicillin well within several weeks after the reaction has subsided. The very rare case that develops prolonged or permanent sensitivity to penicillin can be readily diagnosed in most cases by the presence of positive intradermal or patch tests. In the presence of such positive tests further use of penicillin is definitely contraindicated. From the limited data now available in the literature, aureomycin in doses of 4 Gm. a day for ten to fourteen days can be tried when penicillin is not tolerated or has failed to check the infection.

The foregoing suggested treatment of syphilis, with the exception of aureomycin therapy, is based on evidence which still leaves much to be desired but which is far superior to any published data on the follow up of patients given prolonged metal therapy for syphilis. True, numerous skeptics of the rapid treatment of syphilis can still be found. In my experience, however, the skepticism is based on opinion rather than on factual data. Penicillin is not a panacea for every case of syphilis. In fact no such panacea exists. In medicine it is folly to think in absolute terms. An occasional patient still dies of penicillin-treated pneumococcus pneumonia in spite of the fact that penicillin is an accepted treatment for that infection.

The evaluation of therapy for syphilis is vastly more difficult than that of any acute disease and syphilologists have long been wary of speaking about cures of syphilis. Yet I have heard the statement made by a prominent authority on syphilis for whose judgment I have great respect that early syphilis was cured by good prolonged metal therapy in 95 to 98 per cent of cases. He failed to define what he meant by good prolonged metal therapy. Possibly he meant the amount and kind of metal therapy that would cure 95 to 98 per cent of cases and I defy anyone to define such therapy which was well tolerated by 95 per cent of patients.

The same authority, who believed that 95 to 98 per cent of cases of early syphilis could be cured by good prolonged metal therapy, subsequently declared that it takes twenty years to evaluate a new therapy of syphilis. Why twenty years rather than thirty or forty years? It is well known that gummas have occurred in previously asymptomatic cases of syphilis more than thirty years after infection. To my knowledge the extremely voluminous literature on syphilis does not contain

data on a twenty year follow up of large series of treated syphilitic cases and I do not believe that we must wait twenty years before deciding that penicillin is far superior to metal therapy in the treatment of syphilis. Such data as have been published in this country on the prolonged treatment of early syphilis show that the great majority of clinic patients failed to receive regular injections of bismuth or arsenicals, that as high as 42 per cent of patients irregularly treated for early syphilis relapsed[1] and that nothing like 95 per cent of the patients started on prolonged metal therapy of early syphilis were seronegative 5 years later. In 1940 Padget[2] from the Johns Hopkins Hospital clinic reported on 551 patients originally given some treatment with arsenic and bismuth for darkfield positive early syphilis and examined five to ten years later. Only 65.7 per cent of this series were seronegative and 12.3 per cent were found to have neurosyphilis.

As physicians we are rightly taught to be conservative in making judgments. Skepticism of new remedies and theories is fundamental in scientific medicine. But unsupported statements regarding the advantages of older methods of therapy are not evidence of conservatism or of a scientific turn of mind. The fact is that the older forms of metal therapy for syphilis were highly unsatisfactory in practice for numerous reasons which it is unnecessary to enumerate here. I will, however, take the time to state that since 1937 at Bellevue Hospital we have given fever or penicillin therapy to over 1000 cases of active neurosyphilis as proved by spinal fluid examinations and that over 50 per cent of these patients had had previous metal therapy, in some cases for years, without arrest of the central nervous system infection for a period of more than one year after the metal therapy was stopped. Unfortunately we do not have regular follow-up data for ten years on more than samples of large series of patients treated for neurosyphilis with fever but we have abundant evidence that fever therapy was far superior to metal therapy in the treatment of all forms of neurosyphilis. The follow up of patients treated for active neurosyphilis with penicillin is necessarily less than ten years but I have no hesitancy in stating that, from our experience at Bellevue Hospital, with possible rare exceptions, penicillin is every bit as effective in the treatment of neurosyphilis as malaria therapy. Neither fever therapy nor any other known treatment will restore normal function to permanently damaged nerve tissue but, as I will show later, the activity of neurosyphilis can usually

be determined by spinal fluid examinations and in the experience of Dattner while he was in Vienna and since he came to this country he has never observed relapses of neurosyphilis more than two years after therapy had reduced the infection to inactivity. My more limited experience accords with that of Dattner, yet our observations have been repeatedly challenged by experienced syphilologists who claim to have observed relapses many years after treatment. Only the prolonged follow up of large series of cases for as many years as possible can settle such controversial questions and we are making every effort at Bellevue Hospital to secure such a follow up on patients treated in the thirties with fever therapy and those treated more recently with penicillin.

No one questions that, while the modern treatment of syphilis is becoming relatively simple, the disease itself continues to be extremely complex and treacherous. Many problems in syphilis remain unsolved and we do not yet have an adequate understanding of the disease. It would be a council of despair, however, to refuse to accept a new treatment until we had twenty years of experience with it. It is obviously highly important to follow as many patients as possible for as many years as possible after treatment of syphilis. Data collected in this manner will help to solve some of the present controversies. But, in my opinion, the failure frequently encountered during the years when many patients had irregular metal therapy, spaced at intervals sometimes for ten or more years, gave an erroneous concept regarding the possibility of curing or permanently arresting syphilitic inflammation.

As with other chronic inflammatory diseases, the physician treating syphilis must try to determine whether or not the disease is active. No competent physician would treat healed tuberculosis with scar tissue in the lungs in the same manner as active tuberculosis. Similarly the cardiologist uses every means at his disposal to distinguish between active and inactive rheumatic carditis. In syphilis we are confronted with the same problem. Unfortunately, however, with the exception of early acute syphilis and neurosyphilis, the means of distinguishing between active and inactive syphilis are more limited than in the case of tuberculosis or rheumatic heart disease. Blood serologic tests for syphilis are a poor guide to the activity of the infection in late cases. It has been known for many years that serologic tests for syphilis continue to be positive for long periods after the infection has apparently been ar-

rested by treatment. As long as thirty years ago Moore and Stokes warned the medical profession against the continued treatment of late syphilis merely because of the persistence of positive serologic tests. We now know that seronegativity cannot be obtained in at least 70 per cent of patients for ten or more years after the onset of treatment for late syphilis. Yet this fact is not yet appreciated by a great many physicians who continue to give antisyphilitic treatment of some kind at intervals for years as long as the blood tests for syphilis are positive. I recently saw a patient who had always been asymptomatic so far as syphilis is concerned but a positive serologic test for syphilis was discovered in 1939. He received over 100 injections of arsenic and 100 of bismuth up to 1944 when he was given a relatively small amount of penicillin. In 1945 he was given two courses of 6,000,000 units of penicillin, in 1946 one course of 10,000,000 and another of 6,000,000 units and in 1947, 1948 and 1949 the same courses were repeated. In 1950 he still had a 3+ Kahn test and was advised to take more penicillin.

This case is somewhat extreme but it is by no means exceptional for patients to be advised to receive some kind of antisyphilitic treatment each year until the blood tests for syphilis become negative. Such management of patients in this day and generation is actually malpractice. Sensitive patients are thereby kept in a constant state of anxiety and sometimes in debt because of the presence of a substance called reagin in their blood serum that continues to be found long after the syphilis is inactive and occasionally when syphilis was never even present.

Like metal therapy of syphilis, serologic tests for syphilis are far from satisfactory but as long as we had no better treatment of syphilis arsenic and bismuth had to be used and we are still reliant on serologic tests for diagnosis in many cases of syphilis. Until we learn more about reagin or until other tests are available, the present serologic tests for syphilis must continue to be of paramount importance but we should recognize their limitations.

Apart from neurosyphilis, gummas and active inflammations of the bones, it is extremely difficult to differentiate between activity and inactivity in late cases of syphilis. This is especially true of latent syphilis and cardiovascular syphilis. We cannot afford to neglect so-called latent syphilis; treatment is imperative in such cases but we have abundant reason to believe that latent syphilis can be permanently arrested more

easily than neurosyphilis. Treatment that arrests neurosyphilis should be more than adequate for most cases of latent syphilis. Where cardiovascular syphilis is concerned, no antisyphilitic treatment will cause a dilated aorta to shrink nor stop aortic regurgitation when it has already been established. Antisyphilitic treatment will usually check the inflammatory process but healing occurs with scar tissue which is permanent. In treated cases of cardiovascular syphilis it is usually impossible to know absolutely whether or not syphilitic inflammation is still present. All that we can do in such cases at present is to give treatment which is known to have provided good results in neurosyphilis and other types of late syphilis such as gummas or infections of the bones.

Fortunately, as previously mentioned, the spinal fluid examination provides reliable information regarding the activity of neurosyphilis in the great majority of cases. An increased cell count associated with positive specific tests for syphilis of the spinal fluid, with possible rare exceptions, represents syphilitic inflammation in the central nervous system. Activity is also demonstrated by increased total protein in the spinal fluid. A so-called inactive case of neurosyphilis (as demonstrated by positive spinal fluid specific tests for syphilis, normal cell counts and total protein) may subsequently relapse to activity. Following treatment of active neurosyphilis, inactivity is demonstrated by declining titers of the complement fixation test for syphilis of the spinal fluid, normal cell counts and total protein. Pleocytosis should disappear within three or four months after therapy and increased total protein determinations should show a gradual but steady decline to normal values within a year. Re-treatment is essential if the cell count fails to become normal within three to four months after therapy or if other abnormal values of the spinal fluid tests fail to show improvement. Relapses are indicated by a recurrence of pleocytosis and rising values in other tests.

On the basis of spinal fluid examinations made at six months' intervals we have found at Bellevue Hospital that from six to nine million units of penicillin given over a period of fifteen days has arrested all types of active neurosyphilis for a period of more than three years in over 90 per cent of 166 patients. As previously mentioned, from experience with a much longer period of follow up after malaria therapy for neurosyphilis, Dattner and I are convinced that neurosyphilis rarely, if ever, relapses more than two years after the spinal fluid examination indicates inactivity.

Although quantitative blood tests for syphilis are a much less reliable guide to the activity of late syphilis than are the spinal fluid examinations in neurosyphilis, they are useful. In general, high titers will show a gradual fall to lower levels within a year after successful therapy of late syphilis but fluctuations in titers frequently occur for reasons which I cannot as yet explain. Low titers at the time of treatment, as a rule, show little change for many years after the treatment of late syphilis. Exceptions to these general rules are not infrequent. There is no relationship between the amount of reagin found in the blood and the severity of the disease. Syphilis can be very active in the presence of low titers. The amount of reagin in the blood is no guide to the amount of syphilitic inflammation present. Quantitative tests are of value in each individual only when made serially over a period of years. Sharp sustained rises in previously low titers are usually an indication for re-treatment but a single rise in titer does not prove relapse. Only sustained rising titers can cause suspicion of relapse when there is no other indication of activity. The variations in reagin formation in different individuals is great and I am increasingly puzzled regarding the meaning of reagin in blood serum. In reviewing cases that have been under observation for years many questions arise and I do not have the answer to most of them.

Why, for example, should some 15 per cent of patients treated for secondary syphilis continue to have low reagin titers of the blood for many months longer than is found in the other 85 per cent? I have known rare patients treated for secondary syphilis to have low reagin titers for more than four years and re-treatment with arsenic and bismuth or penicillin had no effect on the titers. Do such patients continue to harbor foci of infection? In my opinion they do not. If one chooses to differ with this opinion, one is certainly entitled to do so, but I can provide much evidence that continued antisyphilitic treatment will not alter the blood tests in such cases. Nevertheless, it is highly important to continue observing such patients for years, if we are to establish the opinion that further therapy is unnecessary and unjustified.

I have frequently heard that we have no proof of cure of early syphilis even after the serologic tests for syphilis have become negative and remained negative for several years. That statement is true in rare cases but it should not throw doubt on the rule that seronegativity over a period of years usually means cure. Active syphilis in the presence

of negative serologic tests for syphilis is definitely rare in my experience. Patients may relapse or become reinfected after the serologic tests for syphilis have become negative but such occurrences are usually demonstrated by the serologic tests. I recently heard of a case of proved syphilitic aortitis in a patient who had been seronegative for years after treatment of early syphilis. I do not question the authenticity of this report but I know that such cases are extremely rare; they are the exceptions that prove the rule. Too frequently we are inclined to exaggerate the importance of exceptions and hence become doubtful about the rule. Few, if any rules in life, are absolute but we still need rules in the practical business of living, and the rules I have attempted to give today are based on experience.

In this paper I have not attempted to give detailed statistics regarding the results of penicillin therapy but such data can readily be found in the literature. There are still differences of opinion regarding the ultimate effects of penicillin therapy and the data now available do not show 100 per cent effectiveness for any known type of antisyphilitic therapy but I am convinced that the schedules of penicillin therapy outlined at the beginning of this paper afford reasonably good treatment for the great majority of syphilitic patients.

REFERENCES

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2. Padget, P. Long-term results in the treatment of early syphilis, *Amer. J. Syph. Gonor. Vener. Dis. 24*:692-731, 1940.

LIBRARY NOTES

SPECIAL INFORMATION CIRCULARS ABOUT THE ACADEMY LIBRARY

A brief outline of current general information about the Academy Library appeared in the Academy's *Bulletin* for February 1951. More details concerning some of its departments and activities are furnished in five "Special Information Circulars," the text of which appears here. Users of the Library are invited to ask questions when anything is not clear to them and to make suggestions for improvment. Separate copies of the circulars and of the general information folder may be had on request.

CIRCULAR NO. 1, "THE REFERENCE AND CIRCULATION DEPARTMENT," indicates briefly the materials which may be found on the open shelves of the Reading Room and Library Lobby, where readers may consult them freely. It also gives instructions for securing books from the stacks and for using the card catalogue. The latter is a complicated tool, but it does contain a wealth of information if one knows the key.

1. *OPEN SHELF MATERIAL.* In the Main Reading Room readers may use the volumes on the shelves without making call-slips. These consist of the most used journals, usually from 1940 to date, but in a few cases from earlier years. A list of the titles kept here may be consulted at the Loan Desk or in a file-tray on the first table in the Reading Room opposite the Loan Desk. The journals are arranged in a single alphabet according to the important words of the title regardless of language or subject and ignoring articles, prepositions, and conjunctions. A few of the most used encyclopedias and systems of medicine are shelved at the east end of the room.

In the Reference Lobby, above and below the card-catalogues are a few general reference works: a selection of dictionaries, general and medical (foreign language dictionaries are so much in demand that call-slips must be presented for them at the Desk); directories; general indexes and major abstract journals; medical, chemical, and biological. For any of the volumes removed from these shelves for use in other rooms, call-slips should be filed at the Loan Desk. Sets of the *Quarterly Cumulative Index Medicus* (known as "QCIM"), of the *Current List of Medical Literature*, and of the *Index-Catalogue* of the Army Medical Library will be found on tables near the entrance.

2. *BOOKS FROM THE STACKS.* Signed call-slips (*Yellow* for periodicals . . .; White for all other types of material) must be presented for books from the main collection housed in the stacks. Before giving them in at the Loan Desk, correct information for the slips should be secured from the card-catalogue, and titles should not be abbreviated. The Desk attendant will give a number to each reader as he hands in slips; this number will show on the call board back of the Loan Desk when the books have ar-

rived from the stacks. No more than five books may be requested at one time. These should be returned to the desk when readers finish with them.

For material in the Rare Book Room (usually bearing a call-mark including the letters "RB"), call-slips should be presented in that Room.

3. *RESERVATION OF BOOKS.* Readers wanting to use the same books for more than one day may have them held, on request, at the Loan Desk. They will be kept 48 hours, if not asked for by others, being thereafter returned to the stacks. Fellows of the Academy may retain books on a special shelf in the Hartwell Room for two weeks.

4. *CARD-CATALOGUE.* The Library's card-catalogue contains entries for the monographs, textbooks, periodical titles, documents, reports, pamphlets, and theses* which the Library possesses. It does *not* contain entries for *journal articles*, as a rule, these must be found through the various periodical indexes, abstract journals, yearbooks, etc. Any library assistant will be glad to direct readers to these. The card-catalogue is divided into two parts: a subject catalogue and a name-and-title catalogue.

Subject Catalogue. This contains entries under all the subjects that are needed to show the contents of monographs, textbooks, and so on, which are in the Library. Entries on *white* cards give the actual references: entries on *blue* cards are cross references: Those which say, "See" such and such, lead one from a heading not used to the one under which the material will be found. Those saying, "See also," lead one to related headings under which additional material on the same subject may be found.

Name-and-Title Catalogue. This catalogue is primarily for authors' names, but it contains also entries for titles of books (though seldom), journals, and series, for institutions, organizations, and firms. Here, too, blue cards are also used for "See" and "See also" cross-references, but they have an additional use as well.

The works of a single author, whether he be an individual or an organization, are entered on *white* cards. If this author has edited or translated books or is the subject of a biography or has some connection with a publication, *blue* cards for these books will be found following his white "author" cards. Then if he wrote in conjunction with others and is the first author named on the title-page, *white* cards for these volumes will follow the above mentioned "added entries." If he is not the first author named, his entry will be on one of the blue cards. For some authors there will be a yellow card preceding all of these various entries, on which will be noted a few biographical references: this is called an "author authority card" and is used in cases where there is some reason for establishing the identity of the individual concerned—especially necessary for two authors who have the same name.

In the Name-and-Title Catalogue there are two sorts of entries which may be somewhat confusing, those for periodicals and those for analytics.

Periodical entries. Titles of periodicals are given an *orange* card. If the journal is closely connected with an organization, a *white* card, in addition, will stand under the name of the organization. Likewise entries will be made in the Subject Catalogue under the subject matter with which the periodical deals in general and under the type of organization issuing it. Thus, the *Journal of the American Medical Association* will appear in the Name-and-Title Catalogue under: 1) its title, "Journal of the American Medical Association"; 2) its organization, "American Medical Association"; and in the Subject catalogue under: 3) the subject, "Medicine, Periodicals, etc., relating to"; and 4) the form heading, "Societies, Medical, by localities, United States." One must remember, however, that the *articles contained in* the periodicals will *not* be found in the card-catalogue, but only in the printed periodical indexes.

Analytical entries. Analytical entries are those made for a part of a book or journal. Obviously, the book or journal will stand on its shelf under its own author or title, and to request it one must give on the call-slip the class-mark and main entry for the book.

* The Library possesses many theses which are not yet catalogued. If a thesis is sought, and not found in the catalogue, a reference assistant should be asked to look it up.

This main entry has been indicated on the cards for analytics by various rubber stamps or other markings: "Give this author, title, and date"; "Ask for," with a red line pointing to the entry to be cited; Copy this on slip," pointing to the main entry.

Reference assistants will be glad to assist readers in the use of the catalogue.

CIRCULAR NO. 2, "THE CURRENT PERIODICALS ROOM," gives a brief notion of the journals kept there and the sort of information which may be had from and about them. Some of the most used indexes are mentioned, together with additional reference tools which are helpful with periodicals.

1. *CURRENT PERIODICALS.* In the Current Periodicals Room are found the current issues of some 1400 journals, all that can be accommodated on the open shelves, arranged in one continuous alphabet, just as they are in the Main Reading Room, except for the Russian titles. These are of course only a part of the 2,200 periodicals regularly received by the Library. These current numbers do not circulate until after they are bound, when they are transferred to the Main Reading Room or stacks. In the Periodicals Room are shelved also the latest announcements of medical schools approved by the American Medical Association.

2. *INDEXES TO CURRENT JOURNALS.* Here are shelved also the various indexes to the current journals:

Quarterly Cumulative Index Medicus (a combined author- and subject-index to articles in the important current journals)

Current List of Medical Literature (a monthly record of the contents of the current journals, arranged under the titles of the journals. Monthly subject- and author-indexes aid the user to find specific articles)

Index to Dental Literature (a combined author- and subject-index to the articles in dental journals published in English)

Index of Current Hospital Literature

Index to Current Periodical Literature on Neoplastic Diseases

Agricultural Index (an author- and subject-index to the articles on agriculture, veterinary medicine, etc., appearing in journals and in agricultural experiment station publications)

Readers' Guide (an author- and subject-index to the more popular magazines)

3. *ABSTRACT JOURNALS.* Publications which supplement the index journals are those containing abstracts. There are many of these, some for general medicine, some for its specialties, and some for the allied scientific fields. Specimen titles are:

Excerpta Medica (issued in fifteen subject sections in English)

Abstracts of World Medicine

Abstracts of World Surgery

Cancer Current Literature

Chemical Abstracts

A card list by subject of the main abstract journals and of the abstract sections of other journals is available.

4. *REFERENCE WORKS FOR SERIAL PUBLICATIONS.* Books may be found here which give information about the periodicals themselves, instead of indexing the articles contained in them. Some of the important ones are:

Union List of Serials (which lists all the important periodicals in American libraries, indicating what libraries possess each)

International Congresses and Conferences, 1840-1937 (supplemented to some extent by a current list maintained by the Periodicals Department)

List of the Serial Publications of Foreign Governments 1815-1931 (listing the bulletins, reports, etc., issued by foreign countries, but *not* those by *cities*)

Periodicals Directory (Ulrich)

N. Y. Special Libraries Association Union List of Periodicals in Special Libraries of the N. Y. Metropolitan District

American Chemical Society. *List of Periodicals Abstracted by Chemical Abstracts* (giving location of chemical journals in libraries of the United States; revised periodically).

5. *SPECIAL CARD LISTS.* Various helpful card-lists compiled by the Periodicals Department may be consulted here: Current periodicals arranged by subject; Foreign periodicals arranged by country;

State and county medical and dental journals arranged by state.

A selected list of English language periodicals received each day is regularly posted as soon as they have been shelved.

In CIRCULAR NO. 3, "THE RARE BOOK and HISTORY ROOMS," will be found a short description of the various materials available there, of the special indexes and catalogues which have been built up to aid in their use, and of the widely representative reference collection of histories and bibliographies which facilitates study of the early works.

These Rooms are open to everyone Monday through Friday, 9 A.M. to 5 P.M. They are closed to everyone on Saturday, Sunday, and holidays, as well as all evenings. The rare books themselves do not circulate, but the books on the open shelves not in constant demand may be taken out by qualified borrowers. If volumes from the open shelves are wanted for use on a Saturday, advance notification will ensure their being available on that day at the Loan Desk in the Main Library.

1. *RESOURCES.*

A. RARE OR HISTORICALLY IMPORTANT MATERIAL OF ANY DATE, in addition to:

All books in the Library published before 1601

All books published in the British Isles before 1701

All books published in America before 1801

All manuscripts, including autograph letters and documents, lecture notes, day-books

Certificates and diplomas

Some 10,000 mounted portraits of medical men and women, and thousands more of illustrations of all sorts of medical subjects in books

Original minutes of medical societies, especially local ones

Lantern slides on historical subjects

Medals struck in honor of physicians or of important occasions

Postage stamps commemorating physicians and events

Early medical instruments and apparatus.

All of the Library's materials dealing with the historical aspects of medicine is kept here, with the exception of later reprints of the early texts and facsimiles, which are stored in the main stacks and should be asked for through the main Loan Desk.

B. REFERENCE TOOLS. These consist of histories, collected biographies and bibliographies of medicine and the allied sciences. They deal with general history in various localities and eras, and with the history of special subjects and institutions or groups of individuals. The bibliographies may list publications by period, subject or locality. All of them on the open shelves may be used without making call-slips, unless they are to be taken out.

2. *CATALOGUES.*

A general card-catalogue of the Rare Book Room materials is available here (with the same entries repeated also in the card-catalogue of the Main Library). A number of supplementary card indexes furnish keys to various special aspects of the historical and rare book material:

A list of the illustrations appearing in the early books and in some of the histories, arranged by the subject portrayed

A chronological list of the rare books by date of publication

A partial list of the rare books arranged by the names of their printers

A partial list of the rare books arranged by the place of publication

A partial list of individuals in any way connected with the rare books, such as former owners, writers of verses or introductory material, persons to whom the books were dedicated, or writers of autograph inscriptions

A partial list of artists responsible for the illustrations in the early books

Partial records of physicians to famous persons, listed under the latters' names.

3. *ASSISTANCE TO READERS.*

Assistance will be given by the Library staff in the use of the various special lists and indexes for such purposes as tracing references to the earliest descriptions of particular diseases, instruments, treatment, and so on, or helping to elucidate old forms

of Latin, French, or German, or medieval abbreviations. They will also advise inquirers on the proper form of name to use for early physicians, Latin or vernacular, or on the usual method of citing early references.

CIRCULAR NO. 4, "BIOGRAPHICAL SOURCES," is intended to assist anyone who needs information about the life and circumstances of any medical individual. It mentions the various sorts of biographical materials in the Library, their location, and the keys to them, together with a brief outline of general procedure for using them. A supplement to this Circular No. 4 supplies a "Selected list of published sources for medical biographies of modern times," giving the frequently consulted sources arranged by countries for easy use.

1. *COLLECTED BIOGRAPHIES.* These comprise the biographical dictionaries, directories, and collections of essays on three or more individuals. Lists of these, arranged by country, may be located in the Subject Catalogue under the headings: "Biography, by localities" and "Biography, Medical, by localities." For the classified books on biography as they stand on the shelves, see as follows:

A. For the modern period:

1. Collected biographies and biographical dictionaries (S.3) shelved in Room 32

2. American directories (S.2.A.A.) shelved in Room 32

3. British directories (S.2.H.A.) shelved in Room 34

4. Other foreign directories (S.2.A.B.) shelved in Room 33.

B. For earlier periods:

Collected biographies (RB.3) on the open shelves in the Rare Book Room.

A selected list of published sources for biographical information for modern times is appended to this circular. Readers will be directed to similar sources for earlier periods upon application in the Rare Book Room. If the modern works cited are not sufficient, aid should be sought from one of the Reference Assistants.

2. *INDIVIDUAL BIOGRAPHIES.* These (S.4) are shelved in the Hartwell Room, arranged alphabetically by the name of the person written about. They may be located in the Name-and-Title Catalogue on the blue cards following the white cards listing an author's works. These blue cards will also give any separate pamphlets and some of the journal articles the Library has about an individual. Some authors will also have yellow "author authority" cards in front of their white cards, on which brief references give the biographical sources from which the form of their names has been established.

3. *PERIODICAL LITERATURE.* A vast reservoir of biographical material exists in the periodical literature, the key to which is furnished by various indexes, some printed, some on cards:

A. Printed: 1) *Index-Catalogue* of the Army Medical Library

2) *Quarterly Cumulative Index Medicus*[*]

3) Indexes to the outstanding national journals of each country, such as *Journal of the American Medical Association, British Medical Journal, Lancet, Deutsche medizinische Wochenschrift, Presse médicale, Riforma medica,* etc.

B. Card files: 1) the Library's "Portrait Index," a list of some 120,000 portraits of medical individuals, indexing not only the portraits but also the biographies accompanying them.

2) the Library's "Biographical File," cumulating in a single alphabet all the biographical references listed in the *Quarterly Cumulative Index Medicus* from 1927 on, as well as notices from other sources.

4. *HISTORIES OF MEDICINE.* These frequently contain biographical data. The ones appropriate for a given person may be located through the Subject Catalogue under such headings as: "Medicine, History of," and "Medicine, History of, by localities," and under the history of particular subjects, such as "Malaria, History and statistics of."

5. *HISTORIES OF INSTITUTIONS, ORGANIZATIONS, etc.* Biographical data likewise appears in the histories of institutions and organizations. If one knows the organizations with which a given individual

[*] Note that the biographical entries from the QCIM from 1927 on have been included in the "Biographical File"; later to be described, so that the volumes of this *Index* will only need to be consulted for information *prior to* 1927.

was connected, histories of them will appear, if the Library has any, on blue cards following the organization's white-card entries in the Name-and-Title Catalogue and also in the *Index-Catalogue* of the Army Medical Library.

6. *OUTLINE OF PROCEDURE.* In looking for brief information on an individual, one might proceed to search as follows:

A. "Portrait Index" (on cards)

B. "Biographical File" (on cards)

C. Name-and-Title Catalogue (blue cards and yellow "author authority card")

D. *Index-Catalogue* of the Army Medical Library

E. Collected biographies and other sources indicated above.

Supplement to Circular No. 4

A SELECTED LIST OF PUBLISHED SOURCES FOR MEDICAL BIOGRAPHIES OF MODERN TIMES

This list is intended simply to indicate some of the most useful sources of information for medical biographies of modern times. It does not attempt to cover all the possible channels of inquiry.

The dates given for published items are those of the latest editions on file in the Library.

GENERAL

1. Biographisches Lexikon der hervorragenden Ärzte der letzten fünfzig Jahre (Fischer). 1932-1933 ..... (S.3.)
2. Biographisches Lexikon der hervorragenden Ärzte aller Zeiten und Völker (Hirsch). (1884-1935) ..... (S.3.)
3. Gubernatis, A. Dictionnaire international des écrivains du jour. 1891 ..... (S.3.)
4. Hyamson, A. M. A dictionary of universal biography of all races and all people. 1916 ..... (S.3.)
5. Index biologorum (Hirsch). 1928 (S.3.)
6. Index generalis. 1939 ..... (S.118.)
7. Index-catalogue of the Library of the Surgeon-General's office, series 1-4. (S.1.)
8. International Surgical Association. Index des titres et publications des membres. 1933-1934 ..... (S.3.)
9. International who's who. 1947 ..... (S.3.)
10. Minerva. Handbuch der gelehrten Welt. 1938 ..... (S.118.)
11. Poggendorff, J. C. Biographisch-literarisches Handwörterbuch 1863-1940. (S.3.)
12. Vapereau, L. G. Dictionnaire universel des contemporains. 1893-1895 ..... (S.3.)
13. Who's important in medicine. 1945 (S.3.)
14. Who's who in world medicine. 1939 (S.3.)
15. World biography. 1949 ..... (S.3.)
16. World of learning. 1948 ..... (S.118)

UNITED STATES

17. American Association for the Advancement of Science. Summarized proceedings and directory 1948 ..... (S.2.)
18. American medical directory. 1950. ..... (S.2.A.A.)
19. American men of science. 1949 ..... (S.3.)
20. Dictionary of American biography. 1928-1944 ..... (S.3.)
21. Dictionary of American scholars. 1942 ..... (S.3.)
22. Dictionary of medical specialists certified by American boards. 1949 (S.2.A.A.)
23. Kelly, T. A. & Burrage, W. L. Dictionary of American medical biography. 1928 ..... (S.3.)
24. National cyclopaedia of American biography. 1892-1946 ..... (S.3.)
25. Who's who in America. 1950-51. (S.3.)
26. Who's who in American medicine. 1925. ..... (S.3.)
27. Who's who in the East. 1948 ..... (S.3.)
28. Who's who in New York. 1947 ..... (S.3.)
29. Who's who among physicians and surgeons. 1938 ..... (S.3.)
30. Who was who in America. 1897-1942. 1943-50 ..... (S.3.)

CANADA

31. American medical directory. 1950 ..... (S.2.A.A.)
32. Canadian who's who. 1938/39 ..... (S.3.)
33. Encyclopedia of Canada. 1935-1937. ..... (S.1.B.)
34. Wallace, W. S. The dictionary of Canadian biography. 1945 ..... (S.3.)
35. Who's who and why [in Canada and Newfoundland]. 1920 ..... (S.3.)

FRANCE

36. Académie de Médecine, Paris. Index biographique des membres, 1820-1939. ..... (S.3.)

37. Annuaire médical Palissier. 1939. (S.2.A.B.)
38. Catalogue général de la librairie français (Lorenz) 1840/65-1922/25 (S.1.)
39. Confédération des syndicats médicaux français. Memento Cartier. 1936/37. (S.2.A.B.)
40. Dictionnaire national des contemporains (Imbert). 1936 (S.3.)
41. Guide Rosenwald. 1951 (S.2.A.B.)
42. Institut de France. Académie des sciences. Index biographique, 1666-1939. (S.3.)
43. Larousse, P. A. Larousse du XXe siècle. (S.1.B.)
44. Qui êtes-vous? 1924 (S.3.)

GERMANY

45. Allgemeine deutsche Biographie. 1875-1912 (S.3.)
46. Deutsches Chirurgen-Verzeichnis. 1938. (S.3.)
47. Deutsches Dermatologen-Verzeichnis. 1939 (S.3.)
48. Deutsches Gynäkologen-Verzeichnis. 1939 (S.3.)
49. Deutsches Zahnärzte-Buch und Zahnärzte-Verzeichnis. 1941 (S.2.A.B.)
50. Kürschner's deutscher Gelehrten-Kalender. 1935 (S.3.)
51. Notgemeinschaft der deutschen Wissenschaftler im Ausland. List of displaced German scholars, 1936 (S.3.)
52. Reichsmedizinal-Kalender für Deutschland. 1937 (S.2.A.B.)
53. Verzeichnis der deutschen Ärzte. 1941. (S.2.A.B.)
54. Wer ist's? 1935 (S.3.)

GREAT BRITAIN

55. Dictionary of national biography (up to 1940) (S.3.)
56. Dentists register. 1950 (S.2.A.H.)
57. Medical directory. 1950 (S.2.A.H.)
58. Medical register. 1950 (S.2.A.H.)
59. Medical who's who. 1925 (S.3.)
60. Who's who. 1950 (S.3.)
61. Who was who. 1929-1940 (S.3.)

ITALY

62. Anuario sanitario italiano. 1939. (S.2.A.B.)
63. Qui è? Dizionario degli italiani d'oggi. 1948 (S.3.)

LATIN AMERICAN COUNTRIES

64. Anuario médico-social de Cuba. 1938. (S.2.A.B.)
65. Diccionario biográfico de Chile. 1946/47. (S.3.)
66. Diccionario biográfico del Ecuador. 1928. (S.3.)
67. Diccionario biográfico del Peru. 1943/1944 (S.3.)
68. Directorio médico mexicano. 1946. (S.2.A.B.)
69. Echevarrieta, M. Diccionario biográfico de la República Argentina. 1943 (S.3.)
70. Maia, J. de A. Indice-catálogo médico brasileiro. 1937-1938 (S.1.)
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In CIRCULAR NO. 5, "SPECIAL INFORMATION FILES," will be found brief descriptions of the various compilations made by the Library through the years, usually in card-files, which may be helpful to anyone whose particular inquiry happens to fall within their scope.

Various card-lists have been compiled by the Library Staff and others from time to time, which are valuable sources of information for certain specific types of inquiry.

1. *AMERICAN PUBLICATIONS BY DATE.* This card-list, compiled by WPA workers and located in the Catalogue Department, lists chronologically by year of publication the books in the Library, acquired before 1940, which were published in America prior to 1876.

2. *BOOKPLATES.* Samples of physicians' bookplates can be located through the Subject Catalogue under the heading "Bookplates of individuals." Small collections of bookplates will be found under the heading "Bookplates."

3. *AUTOGRAPHS.* An index to samples of the handwriting of individuals, usually of their signatures, is kept in Room 32.

4. *EXHAUSTIVE SUBJECT BIBLIOGRAPHIES.* The original card-lists compiled for certain monumental bibliographies have been deposited in the Library, as follows:

a. Encephalitis lethargica (to be found through the Subject Catalogue)

b. Pneumoconiosis (to be found through the Subject Catalogue)

c. Poliomyelitis (to be found through the Subject Catalogue)

d. Current references on antibiotics (except penicillin) (to be found in a card file in the Periodicals Room)

5. *LITERARY WORKS BY PHYSICIANS.* A card-list, located in the Catalogue Department, gives references to some thousands of non-medical works by physicians, not all of them present in the Academy's collection.

6. *LITERARY WORKS ABOUT MEDICINE.* Novels, plays, and poetry about medicine and the members of its profession will be found listed in the Subject Catalogue under the following headings:

Fiction, Medical.
Medicine, Plays relating to.
Medicine, Poems relating to.

7. *MEDICAL JOURNALS PUBLISHED IN NEW YORK STATE.* A card-list, located in the Catalogue Department, furnishes the titles of journals published in New York State prior to 1860 and after that date.

8. *MEDICAL JOURNALS PUBLISHED IN THE UNITED STATES BEFORE 1860.* A card-list located in the Rare Book Room.

9. *SECONDHAND BOOKDEALERS IN NEW YORK CITY.* Brief lists of these, for old books and for periodicals, may be had on request of the Reference Department.

10. *A SELECTED LIST OF AMERICAN JOURNALS.* A brief list of representative American medical journals may be had on request. Arranged by subject fields, it gives address and price of each title. Inquire of the Reference Department.

11. *BIBLIOGRAPHIES ON MANY SUBJECTS.* Over 1,000 more or less full lists of references on a large variety of topics have been compiled by the Bibliographical Department through the years. Occasional ones have been kept up to date. These are available for reference in the Library but may not be taken out.

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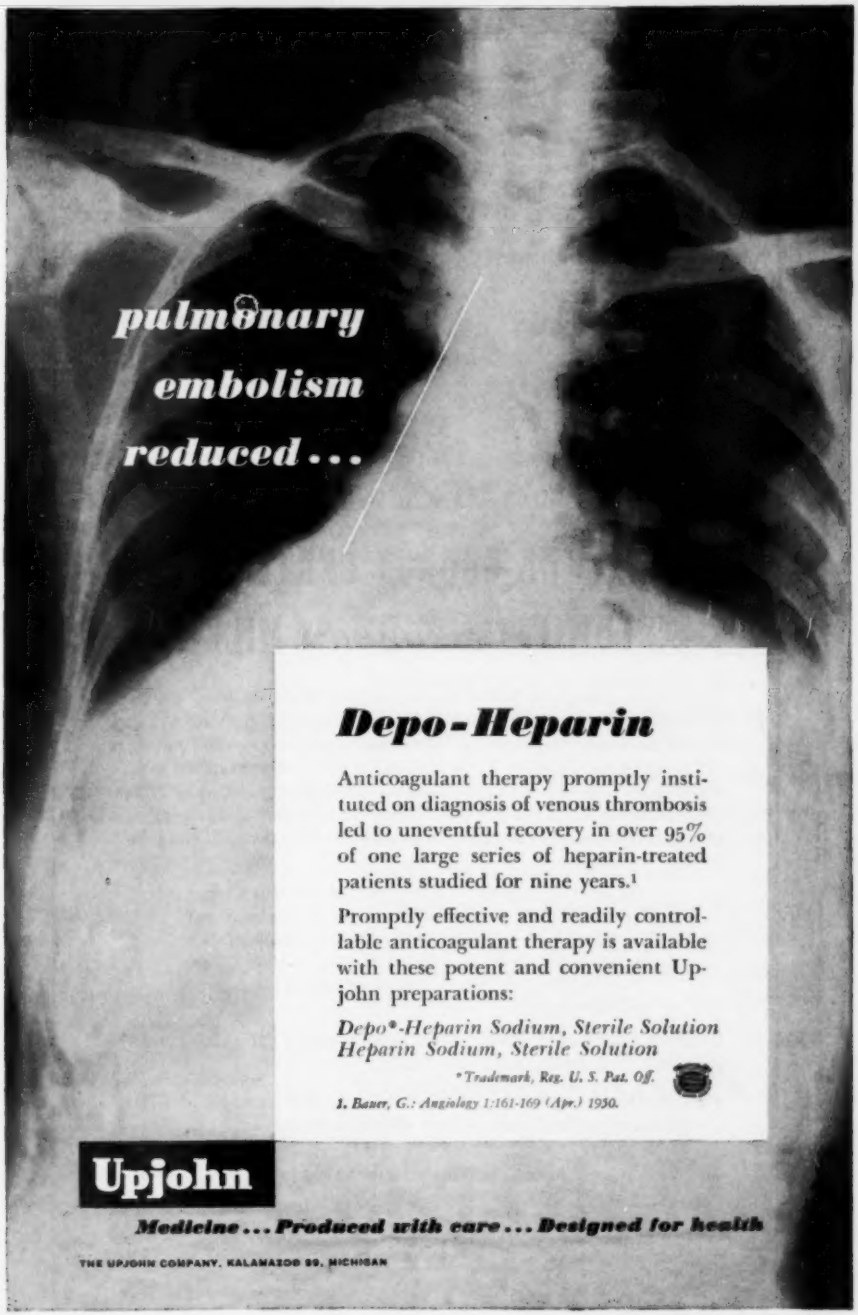

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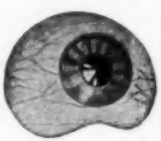

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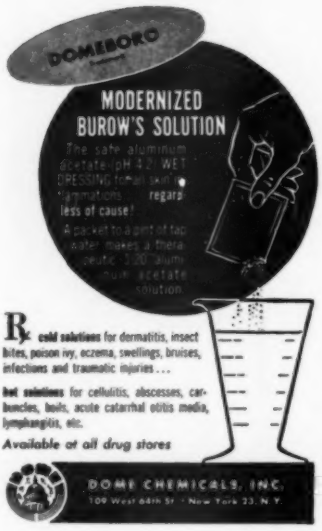
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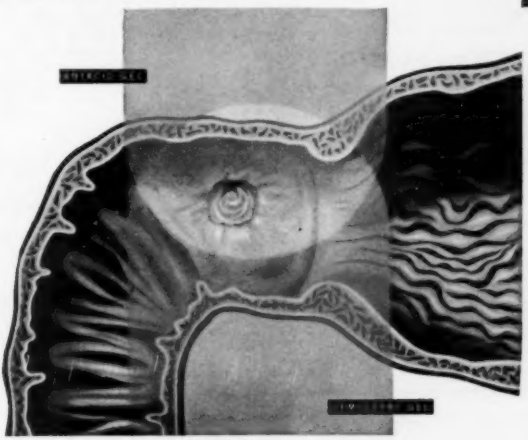

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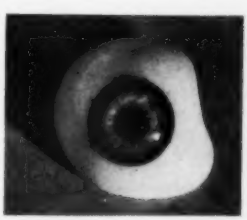

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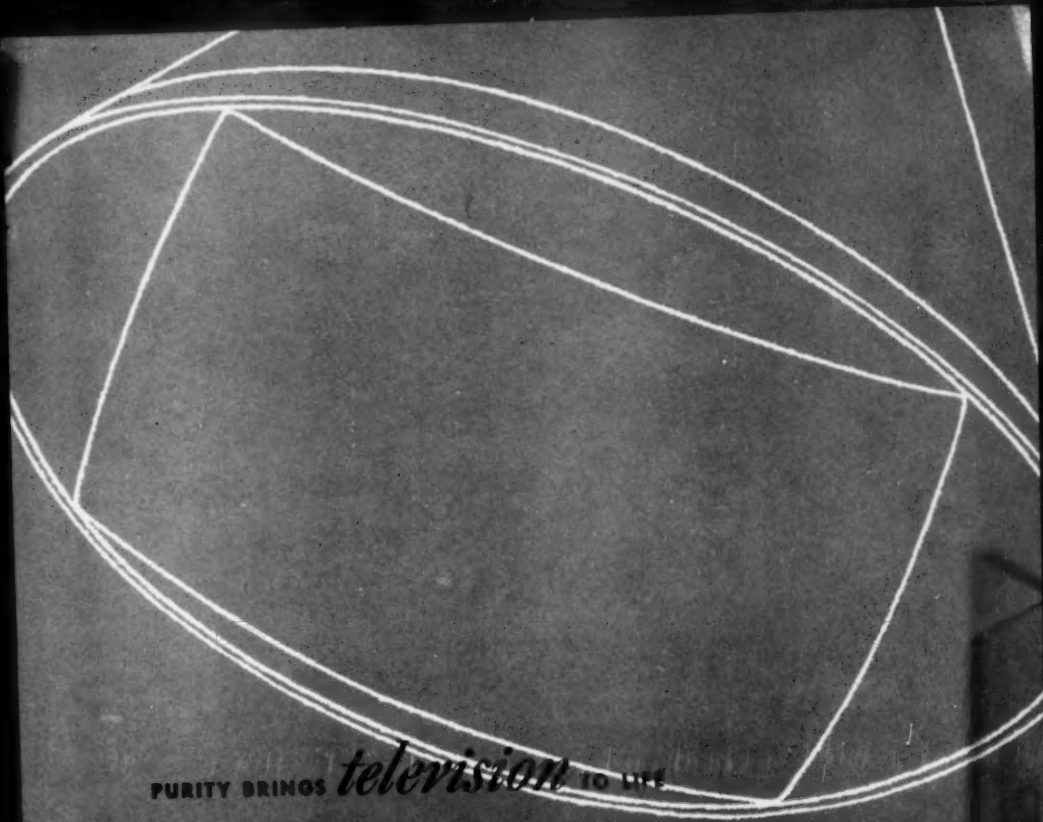

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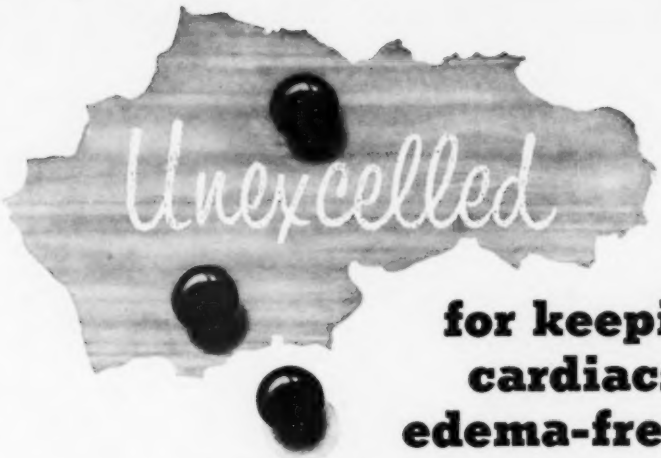

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